78-1118

APPENDIX

IN THE

Supreme Court of the United States

OCTOBER TERM, 1978

No. 1118

PETER H. FORSHAM, ET AL.,
Plaintiff-Petitioners,

v.

JOSEPH A. CALIFANO, JR., ET AL.,
Defendant-Respondents.

On Writ of Certiorari to the United States Court of Appeals For the District of Columbia Circuit

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Petition for Writ of Certiorari filed January 15, 1979
Certiorari Granted May 14, 1979

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INDEX

Page

Exhibits:

Page

RELEVANT DOCKET ENTRIES

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

DATE	NR.	PROCEEDINGS
1975		
Sept 30—		COMPLAINT, appearance; Affidavits (3); P & A's; Exhibits A thru V
	• • •	
Oct 21—		MOTION by pltfs. for expedited relief; c/m
Oct 31—		MOTION by deft. #5 to dismiss and to quash service of process.
	• • •	
Nov 21—		MOTION by federal defts. to dismiss or in the alternative for summary judgment on behalf of the federal defts.; and exhibit 1; exhibit 3.
Nov. 24—		MOTION by pltfs. for leave to file opposition to motion to dismiss; exhibits (2); exhibits B, C, D; c/m.
Dec. 5—		OPPOSITION by pltfs. to defts. motion for summary judgment; motion for summary judgment; memorandum; exhibit A; attachment A,B; exhibit B; c/m 12-4.
Dec 5—		REPLY memorandum by deft. #5 in support of motion to dismiss and to quash service of process; affidavit of Christian R. Klimt; attachment; c/m 12-5.
1976	• • •	
Feb 5—		ORDER denying motion of pltfs. for summary judgment and granting motion of defts. to dismiss. (N) Corcoran, J.
	• • •	

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

1977	
(C)9-14-77—	4-Appellants' motion for further hearing (m-13)

DATE NR. PROCEEDINGS

1977

(T)9-23-77—4-Appellees' opposition to motion for further hearing (m-23)

(T)10-26-77- 4-Appellants' additional allegations to motion for further hearing (m-26) (OK RB)

(T)11-3-77—4-Appellee's (Federal) response to appellants' additional allegations to motion for further hearing (m-3)

(E)11-16-77—Per Curiam order, sua sponte, that the parties to this appeal are directed to file supplemental memoranda, on or before December 5, 1977, addressing the following questions: (see orer for details: Bazelon, CJ, Leventhal and MacKinnon, CJ's

(T)12-5-77—4-Appellee's (Christian Klimt) supplemental memorandum in response to order of 11/16 (m-1)

(T)12-5-77—4-Appellees' (Federal) supplemental memorandum in response to order of 11/16 (m-5)

(T)12-5-77—4-Appellants' supplemental memorandum in response to order of 11/16 (m-5)

1978

(R)7-11-78—Opinion for the Court filed by Circuit Judge Leventhal

(R)7-11-78—Concurring opinion filed by Circuit Judge MacKinnon

(R)7-11-78—Dissenting opinion filed by Circuit Judge Bazelon

• • •

(T)7-25-78—10-Appellants' petition for rehearing and suggestion for rehearing en banc (m-25)

• • •

(R)10-17-78—Statement of Circuit Judge Bazelon as to why he voted for rehearing

• • •

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

CIVIL ACTION NO.:

PETER H. FORSHAM, HENRY DOLGER, HOLBROOK S. SELTZER, as they are members of the Committee on the Care of the Diabetic, *Plaintiffs*,

v.

DAVID MATHEWS, Secretary of the Department of Health, Education, and Welfare
THEODORE COOPER, Assistant Secretary of Health, Department of Health, Education and Welfare
ALEXANDER M. SCHMIDT, Commissioner of the Food and Drug Administration
G. DONALD WHEDON, Director of the National Institute of Arthritis, Metabolism, and Digestive Disease
CHRISTIAN R. KLIMT,
Defendants

COMPLAINT

JURISDICTION

1. This is an action pursuant to the provisions of the Freedom of Information Act (FOIA) 5 U.S.C. § 552, as amended, to enjoin the defendants from withholding reasonably identifiable agency records requested by plaintiffs and to compel the production of such records.

2. This is also an action pursuant to the provisions of 28 U.S.C. §§ 2201-2 for a declaratory judgment that defendants' withholding of records as set forth herein is unauthorized by and contrary to law, and for injunctive and other relief.

3. Jurisdiction of this Court is invoked pursuant to the provisions of 28 U.S.C. § 1331, 5 U.S.C. § 552 and 28 U.S.C.

§§ 2201-2. There exists between the parties an actual controversy, justiciable in character, in respect of which plaintiffs require a declaration of their rights by this Court. The matter in controversy exceeds the sum of $10,000, exclusive of interests and costs.

PARTIES

4. The Committee on the Care of the Diabetic (CCD) is an unincorporated association of 178 physicians in the United States who are involved in the daily management and treatment of diabetes mellitus, a disease affecting millions of Americans. Since its inception in 1970, the primary purpose of CCD has been to assure that both the patients who suffer from diabetes mellitus and the physicians who treat it are provided with full, accurate, and truthful information concerning the safety and efficacy of medications prescribed for its treatment. Plaintiffs, all members of CCD, are as follows:

a. Peter H. Forsham, a resident of Mill Valley, California, is Professor of Medicine and Pediatrics, Director of the Metabolic Research Unit, and Chief of Endocrinology at the University of California Medical Center, School of Medicine, San Francisco, California. He is author of more than two hundred and fifty medical and scientific papers in the field of endocrinology and metabolism, notably diabetes and diseases of the adrenal and pituitary glands. He also is Chairman of The Coordinating Committee of CCD;

b. Henry Dolger, a resident of New York City, New York, is Clinical Professor of Medicine, Attending Physician and Chief of the Diabetes and Pre-Natal Diabetes Clinics at the Mt. Sinai Hospital, New York. He is Consultant in diabetes at Elmhurst General Hospital and Kingsbridge Veterans Hospital. He is also author of "How to Live With Diabetes" and thirty-six other publications and monographs relative to diabetes. He is also a member of The Coordinating Committee of CCD;

c. Holbrook S. Seltzer, a resident of Dallas, Texas is Chief of the Metabolic Section at the Veterans Administration Hospital and a Professor of Internal Medicine at the University of Texas Southwestern Medical School in Dallas. He is the author of a report entitled "A Summary of Criticism of the Findings and Conclusions of the University Group Diabetes Program (UGDP)". He has been involved in the treatment and management of thousands of diabetic patients over the last twenty years and is a member of the Coordinating Committee of CCD.

5. The defendants are as follows:

a. Defendant David Mathews is Secretary of the Department of Health, Education, and Welfare (DHEW) which consists of the Office of the Secretary and the several operating agencies;

b. Defendant Theodore Cooper is Assistant Secretary of Health of DHEW and, as such, is responsible for issuing final administrative decisions based on requests for DHEW records under FOIA.

c. Defendant G. Donald Whedon is Director of the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD), a Division of the National Institutes of Health (NIH), an operating agency within DHEW.

d. Defendant Alexander M. Schmidt is Commissioner of the Food and Drug Administration (FDA), an operating agency within DHEW.

e. Defendant Christian R. Klimt is the Director of the Division of Clinical Investigation at the University of Maryland School of Medicine and Director of the Coordinating Center for the University Group Diabetes Program. In the latter capacity, he is custodian of the records sought below.

STATEMENT OF THE CASE

6. From 1961 to the present, NIAMDD has sponsored and supported a study known as the University Group Diabetes Program (UGDP), whose purpose has been to evaluate the effect of oral hypoglycemic treatment on the management and control of diabetes mellitus. This support has taken the form of a series of initial and supplemental grants to twelve participating clinics in the United States.

7. The UGDP filed its first Notice of Claimed Investigational Exemption for New Drugs (IND) in 1967, five years after enactment of the IND provisions of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(i). A second IND was filed in 1971. (Exhibit U attached)

8. The UGDP has involved more than one thousand subjects whose condition was evaluated at the beginning of the study (baseline) and at three-month intervals thereafter. The results of the tests performed on such subjects were recorded on forms standardized for all twelve clinics, copies of which were forwarded to the UGDP Coordinating Center for storing, processing, and analysis. The UGDP raw data referred to hereafter consist of the forms transmitted to the Coordinating Center and the computer tapes and/or programs on the basis of which analysis was conducted of the data contained in such forms.

9. In December 1970, the UGDP published a report on the first eight years of its research (*Diabetes* Vol. 19; Supp. 2, 1970). The UGDP report suggested a possible relationship between oral hypoglycemic drugs and cardiovascular complications in patients suffering from diabetes mellitus.

10. From 1970 to the present, the FDA has sought to require a relabeling of oral hypoglycemic drugs based on the results of the UGDP.

11. On October 7, 1971, CCD petitioned the FDA to rescind proposed agency action involving relabeling of oral

hypoglycemic drugs and to withhold future action pending independent corroboration of UGDP findings. Alleging that the UGDP contained basic flaws in methodology and conclusions, CCD further requested . . .

> that the Food and Drug Administration make available to your petitioners and other qualified researchers the baseline data of the University Group Diabetes Program; such baseline data shall include the total patient record of each patient included in the study. (Exhibit A attached).

12. In refusing to rescind its action on June 5, 1972, the FDA endorsed the reliability of the UGDP study and urged that it be given serious consideration by the medical profession. In response to CCD's request for access to the UGDP raw data, the FDA stated as follows:

> Your petition states that the results of the UGDP study are not available and therefore not subject to the usual critical review. *We have been assured that the UGDP personnel will honor any reasonable request for data and information.* (Letter of Charles C. Edwards, Commissioner, to Neil L. Chayet, Counsel for CCD, June 5, 1972, p. 8) (Emphasis supplied).

13. On August 11, 1972, CCD brought an action in the United States District Court for the District of Massachusetts (*Bradley* v. *Richardson*, No. 72-2517-M) seeking declaratory and injunctive relief to prevent the FDA from ordering a relabeling of oral hypoglycemic drugs. CCD further requested

> that the Food and Drug Administration make available to the plaintiff physicians the baseline data of the University Group Diabetes Program and that such baseline data include the total patient record of each patient included in the study.

14. On November 3, 1972, the United States District Court issued a preliminary injunction enjoining the FDA-ordered relabeling pending hearing on the merits. The FDA appealed from the granting of the preliminary injunction to the United States Court of Appeals for the First Circuit.

15. On July 31, 1973, the Court remanded the question of drug relabeling to the FDA for further consideration. *Bradley* v. *Weinberger,* 483 F.2d 410 (1st Cir. 1973). Referring to CCD's several requests for access to the UGDP raw data, the Court stated as follows:

> . . . Where the correctness of factual findings are involved or where the complainants request the full record, we think the agency must produce it in court [citing cases]. *Bradley* v. *Weinberger,* 483 F. 2nd 410, fn. 4 (1st Cir. 1973).

16. On October 15, 1974, following the continued unavailability of the raw data to CCD and the disclosure of portions of such data to other parties i.e., a committee of the Biometric Society reviewing the UGDP pursuant to contract with NIAMDD, CCD telegrammed defendant Whedon requesting: (a) a copy of the draft Biometric report; and (b) immediate access to the data (Exhibit C attached).

17. On October 21, 1974, defendant Whedon denied CCD's request for a copy of the draft Biometric report and failed to respond to its request for access to the data (Exhibit D attached).

18. In a letter to FDA General Counsel on November 4, 1974, CCD renewed its request for a copy of the draft Biometric report and for access to the raw data on the basis of both the Freedom of Information Act and the prior disclosure and circulation of such records (Exhibit E attached).

19. On November 11, 1974, FDA General Counsel forwarded CCD's request to General Counsel for the Public Health Service (Exhibit F attached).

20. On November 22, 1974, General Counsel for the Public Health Service forwarded CCD's request to defendant Whedon at NIAMDD (Exhibit G attached).

21. On December 3, 1974, through its Freedom of Information Officer, DHEW again denied CCD's request for a copy of the draft Biometric report and failed to respond to the request for access to the raw data (Exhibit H attached).

22. On January 2, 1975, CCD requested administrative review and reconsideration of the DHEW action of December 3, 1974 (Exhibit I attached).

23. On January 27, 1975, CCD received from defendant Whedon a copy of the *final* Biometric report on the UGDP. Defendant Whedon further stated that "no one in DHEW has ever had any of the raw data of the UGDP study" (Exhibit J attached).

24. From May-August 7, 1975, CCD renewed its requests for the UGDP raw data and the draft Biometric report in exchanges of communication with defendant Cooper in his capacities as DHEW Assistant Secretary for Health and as final administrative authority under the Freedom of Information Act (Exhibits K-N attached). In addition, CCD requested further specific information concerning the UGDP and its investigators (Exhibit O attached), which information, with several exceptions, was provided by NIAMDD (Exhibit P attached).

25. On August 7, 1975, defendant Cooper notified CCD that neither the FDA nor NIH had ever reviewed or seen the UGDP raw data and that proposed FDA relabeling of the oral hypoglycemic drugs was based solely on UGDP publications and the final Biometric report. He further in-

dicated that the raw data was stored in a bank vault in the State of Maryland under the control of defendant Klimt and concluded as follows:

> It appears, therefore, that the raw data is the property of the individual investigators and the coordinating center. Given that this is the case,

WHEREFORE, plaintiffs respectfully pray:

1. That this Court issue an order pursuant to the provisions of 5 U.S.C. § 552, as amended, directing the defendants, David Mathews, Theodore Cooper, Alexander M. Schmidt and G. Donald Whedon, in their respective capacities as Secretary of DHEW, Assistant Secretary for Health, Commissioner of the FDA, and Director of NIAMDD, and defendant Christian R. Klimt, in his capacity as principal investigator of the UGDP study and as custodian of records produced during such study to produce: (1) Raw data of the University Group Diabetes Program, which may be in the possession of any of the defendants or as to which they may have a right of access and which consist of the following: (a) the original data as transmitted to the UGDP Coordinating Center by each of the twelve participating clinics; (b) the computer tapes containing statistical analyses of morbidity and mortality based on such data; (c) the computer programs developed by the UGDP Coordinating Center to carry out the foregoing analyses; and (2) the draft report of the Biometric Committee reviewing the UGDP pursuant to contract with NIAMDD.

2. That this Court issue a declaratory judgment that plaintiffs are entitled to the foregoing records under applicable provisions of law and permanently enjoin the defendants from refusing to produce said records.

3. For such other or further relief as may be appropriate.

Respectfully submitted,

CHAYET AND SONNENREICH, P.C.

By /s/ NEIL L. CHAYET
Neil L. Chayet

/s/ HARVEY W. FREISHTAT
Harvey W. Freishtat

Attorneys for Plaintiffs

6 Fayette Street
Boston, Massachusetts
617/357-0202

VETERANS ADMINISTRATION HOSPITAL

4500 S. Lancaster Road
Dallas, Texas 75216

AFFIDAVIT OF HOLBROOKE S. SELTZER, M.D.

I, Holbrooke S. Seltzer, being duly sworn, hereby depose and say as follows:

I am Chief of the Metabolic Section of the Veterans Administration Hospital and a Professor of Internal Medicine at The University of Texas Southwestern Medical School in Dallas, Texas.

I am a clinician who has spent more than 20 years of his professional life in the close management of more than 1,000 patients with diabetes mellitus.

Since its inception in November, 1970, I have been one of the members of the Coordinating Committee of the Committee on the Care of the Diabetic (CCD), and I have written a report entitled "A Summary of Criticisms of the Findings and Conclusions of the University Group Diabetes Program (UGDP)," which was published in Diabetes, volume 21, pages 976-979, in September, 1972.

Since the first publication of the UGDP findings in 1970, the study has been the subject of great controversy among diabetologists, epidemiologists, cardiologists, pharmacologists, biometricians and mathematicians within the medical and scientific communities. The criticism has focused on the inadequacies of the UGDP in terms of design, methodology, execution, interpretation, and even in matters of integrity. Some of the major criticisms are the following: (1) At least one out of every 14 patients in the study did not even have diabetes. (2) The patients used in some of the 12 treatment centers were much sicker before treatment than those admitted to other clinics; and the centers that enrolled the sickest patients had the highest mortality in all

treatment groups. (3) Actually, the two clinics that enrolled the greatest number of already-sick patients subsequently contributed 40%-50% of all deaths in all four treatment groups. This means that the remaining 50%-60% of deaths distributed throughout the other 10 treatment centers represents an inconsequential finding; in other words, the entire "UGDP Controversy" arose because of execessive mortality in only two of the 12 clinics. (4) A fixed dosage of tolbutamide (Orinase) was used in all tolbutamide-treated patients; since this is never done in clinical practice (the dosage is changed according to the patient's response), this means that some patients were over-dosed and others were under-dosed at various times. (5) In evaluating the results, no attention was paid to other uncontrolled variables that are known to influence cardiovascular mortality (obesity, high blood pressure, high blood cholesterol, smoking history, etc.). The many other criticisms of the UGDP study are summarized in the article cited above.

Fundamentally, all of these criticisms come down to the same roadblock—namely, the unavailability of the raw data for review and examination. If the data were made available for review, they would demonstrate the presence or absence of the 15 indices of pre-existing cardiovascular and non-cardiovascular disease that were obtained on each of the 823 patients before assignment to any of the four original treatment groups.

The unavailability of the data has not been due to oversight, since the CCD has been requesting access to it for four years. I personally discussed the need for such an impartial review with the Biometric Committee on January 9, 1973.

Only via a thorough review of the raw data can the following long-standing questions and criticisms be resolved: (1) What was the frequency of total cardiovascular risk factors (as originally defined in the UGDP progress reports) in each patient in all 12 of the treatment centers? (2) Were

more patients with a greater number of combined cardiovascular risk factors randomly assigned to the tolbutamide-treatment group than to the placebo group or either of the insulin-treated groups? (3) Did the tolbutamide-treated patients who died of cardiovascular causes have greater individual totals of the 8 baseline cardiovascular risk factors (as has been charged) than those who died of cardiovascular disease in the other three treatment groups?

Without such answers I find it difficult to know what to tell my patients about the safety or efficacy of the oral hypoglycemic drugs. That is why I have long been involved in the effort to secure access to the raw data.

It has always seemed to me that the UGDP investigators would themselves have welcomed this opportunity to settle the controversy once and for all, by allowing the raw data to be examined. I know that, as a research scientist who has performed clinical research for 19 years with funds provided by the Veterans Administration and the U. S. Public Health Service (National Institutes of Health), I have always considered it my responsibility to disclose the raw data obtained on subjects and patients to either of these supporting agencies upon request.

However, if access to the raw data continues to be denied by the UGDP investigators to any outside review, than I believe members of the medical community have a responsibility to ensure the accuracy and veracity of the study, particularly when a government agency is proposing to use results of that study to require changes in the management and control of patients with diabetes mellitus.

I continue to hope that, through disclosure of data in the very near future, both physicians and patients will soon have answers to the questions they have long been asking.

/s/ Holbrooke S. Seltzer, M.D.
Holbrooke S. Seltzer, M.D.

September 27, 1975

Then personally appeared before me the above-named Holbrooke S. Seltzer, M.D., and made oath that the contents of the foregoing affidavit are true to the best of his knowledge and belief, and said Holbrooke S. Seltzer, M.D. signed the foregoing affidavit in my presence.

/s/ Arthur F. Herron
Arthur F. Herron
Notary Public

September 27, 1975
Dallas, County, Texas

Affidavit

As the Chairman of the Committee on the Care of the Diabetic, I wish to state as follows: The undersigned, who has been with the Committee since its inception, does not believe in the validity of a number of conclusions drawn by the UGDP investigators. Since he feels that there is a real need for final clarification of the controversial points in the UGDP investigation, he wishes to gain access for the Committee on the original or so-called raw data that were obtained in this study. This is being done in the interest of the diabetic public being treated with oral hypoglycemic agents at this time and in the future.

Since these original data from the study have not been made available to us to date, we have no choice but to invoke the Freedom of Information Act in order to obtain these data, preferably through the National Institutes of Health, who should have access to them at our request.

/s/ Peter H. Forsham
Peter H. Forsham, M.D.
Professor of Medicine and Pediatrics
University of California, San Francisco
and Chairman of the CCD

PHF:kdd

STATE OF CALIFORNIA
COUNTY OF SAN FRANCISCO

On September 26, 1975 before me, the undersigned, a Notary Public in and for said County and State, personally appeared PETER H. FORSHAM, M.D. known to me to be the person whose name is subscribed to the within instrument and acknowledged that he executed the same.

WITNESS my hand and official seal.

/s/ ALICE M. HERRERA
Alice M. Herrera,
Notary Public

List of Exhibits

A—October 7, 1971 Petition of CCD

B—First Circuit Opinion in Bradley v. Weinberger

C—October 15, 1974 telegram to G. Donald Whedon

D—October 18, 1974 telegram from G. Donald Whedon

E—November 4, 1974 letter to Peter Barton Hutt

F—November 11, 1974 letter from Peter Barton Hutt

G—November 22, 1974 letter from Assistant General Counsel for Public Health

H—December 3, 1974 letter from DHEW Freedom of Information Officer

I—January 2, 1975 letter to Charles C. Edwards, Assistant Secretary DHEW and reply

J—January 27, 1975 letter from G. Donald Whedon

K—May 6, 1975 letter to Theodore Cooper

L—May 23, 1975 letter from Theodore Cooper

M—June 3, 1975 letter to Theodore Cooper

N—July 8, 1975 letter to Theodore Cooper

O—July 11, 1975 letter to Linden Neff

P—July 30, 1975 reply from Russell Roberts F.O.I.A. Officer

Q—August 7, 1975 letter from Theodore Cooper

R—August 7, 1975 letter to Theodore Cooper

S—CCD "Statement on the Treatment of Diabetes"

T—UGDP Revised Protocol, 1961

U—September 19, 1975 letter from Sam D. Fine

V—September 26, 1975 letter to Richard Merrill

EXHIBIT A

CHAYET and FLASH
Counsellors at Law

15 Court Square
Boston, Massachusetts 02108

Area Code 617 523-6511

October 7, 1971

Commissioner of Food and Drugs
Department of Health, Education and Welfare
Washington, D.C. 20204

Dear Sir:

I am herewith transmitting a petition relative to the Food and Drug Administration's actions based on the agency's acceptance of and extrapolations from the conclusions of the University Group Diabetes Program.

I would appreciate a prompt reply to this petition and would hope that in any case, one could be received within 30 days.

I anticipate that the petition will be printed in the Federal Register in the usual course. Kindly address your reply to me at the above address.

Very truly yours,

/s/ NEIL L. CHAYET
Neil L. Chayet

NLC:mm

Commissioner of Food and Drugs
Department of Health, Education, and Welfare
Washington, D.C. 20204

Dear Sir:

This petition is submitted with respect to (1) the issuance of recommendations contained in the October, 1970 FDA Current Drug Information Bulletin entitled, "Diabetes Prescribing Information" and (2) the recommended changing of the INDICATIONS AND WARNINGS section of the labelling of all sulfonylureas as stated in the June 23, 1971, FDA Drug Bulletin.

Attached hereto, in quintuplicate and constituting a part of this petition are the following:

A. The FDA Current Drug Information, October, 1970 (marked Appendix A).

B. Relevant excerpts from FDA Drug Bulletin dated June 23, 1971 (marked Appendix B).

C. Written communications of Robert F. Bradley, M.D. and the Committee on the Care of the Diabetic to the FDA. (marked Appendix C).

D. A statement of the grounds upon which your petitioner relies for the action requested herein (marked Appendix D).

The recommendations which are the subject of this petition have been made by the Food and Drug Administration (FDA) as a result of the report of the University Group Diabetes Program (UGDP). This report has been the subject of intense controversy since its conclusions were made known both because of the unprofessional manner in which the conclusions originally became known, in the lay press, as well as the irreparable flaws of its methodology, and the major inconsistencies in the conclusions. The report, which suggested that tolbutamide is no more effective than diet alone in the treatment of mild adult-onset diabetes, is insupportable in the light of impartial scientific inquiry, and the Food and Drug Administration, by embracing its

conclusions, has intruded into the practice of medicine, placing the physician who continues to prescribe tolbutamide for the treatment of maturity-onset diabetes in jeopardy and causing great concern on the part of more than a million diabetics and their physicians who have regularly used this drug.

This petition is grounded in three fundamental principles:

1. Regardless of the validity of the UGDP study, it is the contention of your petitioners that the Food and Drug Administration's legal mandate is solely the regulation of drugs as to safety and efficacy and not the control of medical or scientific practices; furthermore, the FDA should not engage in the establishment of an official governmental policy in respect to the practice of science or medicine. We believe this to be as true for the treatment of diabetes as it would be in relation to such procedure as cardiac surgery or kidney and heart transplants.

2. The government should particularly refrain from taking a partisan position and establishing a "government line" in an area of medicine and science in which extensive controversy and debate exists among qualified scientists and/or physicians. In the present situation such a position has been taken despite the absence of corroborating studies which have reproduced the UGDP findings, an essential criteria in the establishment of scientific principles. Even if the UGDP study were beyond reproach, which the statement marked "Appendix D" will show it is not, the FDA should not adopt the singular position of one group if contradicting positions are advocated by other qualified scientists and physicians. With respect to the UGDP findings, strong controverting data and extensive comment, disagreement and experience among a large body of

extremely well qualified scientists exists and is a matter of scientific record. Furthermore, in this situation the FDA has ruptured its own rule of fair balance in failing to present the other side of the issue in its mailings and statements, even as it has itself taken sides in the issue.

3. The single study upon which the FDA bases its action has been criticized on professional, scientific, clinical, statistical, and other grounds. Furthermore, FDA action did *not* properly reflect the criticisms and recommendations of its own medical advisory panel on the subject. In effect, despite repeated requests for over a period of a year from many different sources, the basic data of the study remain unavailable to the scientific community and the recent report on phenformin [1] presents an inadequate amount of protocol material to enable adequate scientific evaluation. The 6/23/1971 FDA Current Information Bulletin nevertheless made the general statement that "although this study considered only one sulfonylurea, tolbutamide, it raises serious questions as to the ultimate place of all antidiabetic agents in the treatment of diabetes mellitus."

This petition for a reversal and clarification of the FDA's positions as stated above is thus grounded not only on the basis of the fundamental principle of the separation of science and state, but also on the fact that legitimate scientific controversy exists and the UGDP study has been controverted by a large and leading body of specialists in the field as being more than just erroneous. In point of fact, the FDA has sought in this situation to regulate therapy on the basis of an experiment which is based on

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[1] "Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes," JAMA, August 9, 1971.

faulty methodology, which has disregarded many essential recommendations related to the true *therapeutic* application of the agents under study, and in doing so has extrapolated without valid statistical basis, thus flying directly in the face of the caveat of the authors of the UGDP study themselves, to wit:

> It should be noted that any conclusion reached in this study pertains only to the type of patient studied and to the specific hypoglycemic agents and dosage schedules used. Extrapolation of findings obtained in the UGDP to other dosage schedules of the same drug or to other chemically related hypoglycemic agents not included in this study must be made on a judgmental and nonstatistical basis.[2]

In addition, it was recently reported that Dr. Christian R. Klimt, the statistical coordinator of the UGDP study, stated that a similar trial of diabetic oral agents, which he will be conducting in Yugoslavia under FDA auspices, will employ a flexible dosage regimen and be confined to a symptomatic diabetic population.[3] The use of fixed dosage and asymptomatic patients are two of the serious limiting factors in the UGDP study (see Appendix D). This action by the statistical coordinator indicates the merit of the most serious criticism which has been levelled at the UGDP report.

It has also been reported that the protocol in regard to the double blind technique may not have been followed in every participating clinic for all patients (see Appendix D, Part 2).

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[2] "University Group Diabetes Program," *Diabetes* 19, Supp. 2, 1970.

[3] Drug Trade News, August 23, 1971.

Lastly, it should be noted that the conclusions of the study have been specifically rejected by the Canadian Food and Drug Directorate, the Canadian Diabetes Association, the British Committee on Drug Safety, the British Diabetes Association, the German Ministry of Health, the German Diabetic Society, and the Swedish government.

Failure to grant petitioner's requests will result in a continuance and aggravation of damage which has already been perpetrated by the dissemination of these recommendations already made and the suggested labelling changes. As a result of actions taken by the Food and Drug Administration, an undetermined number of patients stopped taking medication on their own or were taken off the medication by their alarmed physicians and subsequently became symptomatic.

Failure to grant these requests will cause further irreparable harm to more than a million patients, particularly to their relationship with their physicians and to their personal psychic stability so essential in a disease such as diabetes.

Failure to grant the request will perpetuate the unjustified damage done to a large number of physicians and research scientists in the field of diabetes with respect to their standing in the public view as well as in the medical and scientific communities.

The Food and Drug Administration has taken a partisan position in an area of valid and continuing medical and scientific discussion and debate. This is a serious error both in principle and in fact. The Food and Drug Administration indentification with a controversial study which has been subject to extensive criticism is particularly unfortunate.

It must clearly be recognized that the government has no role as a partisan in valid continuing scientific controversy.

Your petitioners, in reliance on the statement contained in Appendix D of this petition, respectfully request that the following steps be taken immediately:

(1) That the recommendations contained in the October 1970 Food and Drug Administration Current Drug Information Bulletin, entitled "Diabetes Prescribing Information" be immediately rescinded and that notice of such rescission be distributed in exactly the same manner as the Bulletin was distributed.

(2) That the recommendations which would change the INDICATIONS AND WARNINGS section of the labelling of all sulfonylure as stated in the June 23, 1971 Food and Drug Administration Drug Bulletin be rescinded and that notice of same be distributed in exactly the same manner as the Bulletin was distributed.

(3) That the Food and Drug Administration use its best efforts to restore the confidence of patients in their physicians who use tolbutamide and the sufonylureas generally.

(4) That pending corroboratory studies the Food and Drug Administration refrain from making any further recommendations related to hypoglycemic substances based on the University Group Diabetes Program and that any actions related to the UGDP studies avoid debatable extrapolations and clearly indicate the study's deficiencies and the controversial nature of its implications. And that any references be made in the context of fair balance as above stated.

(5) That the Food and Drug Administration repudiate all other recommendations, statements, mailings or communications of any kind which have been distributed to the medical and scientific communities, to the lay press, or to the general public based on the UGDP study and that the Food and Drug Administration use its best efforts to widely disseminate such repudiation.

(6) That the Food and Drug Administration make available to your petitioners and other qualified researchers the baseline data of the University Group Diabetes Program; such baseline data shall include the total patient record of each patient included in the study.

(7) That in accord with its policy of fair balance, the Food and Drug Administration disseminate with equal effort, emphasis and frequency, the results of all other studies reported by qualified researchers as well as clinical opinions of outstanding diabetologists which disagree with or controvert UGDP study and the conclusions extrapolated therefrom.

(8) That your petitioners be provided with full and complete answers to the following questions:

(a) By virtue of what statute, regulation, rule, or other legal authority does the Food and Drug Administration establish therapeutic regimens by stating preferences —i.e., first, diet; second, insulin and third, oral agents —in its Bulletins marked Appendix A and Appendix B of this petition?

(b) Why did the Food and Drug Administration ignore the views of the majority of its own Advisory Committee on Diabetes, a committee that was composed of four diabetologists, two biostatisticians and a biochemist? That majority was not willing to accept the conclusions of the UGDP report.

(9) That any other relief be granted that the Food and Drug Administration may deem meet and proper to fulfill the spirit and letter of this petition.

respectfully submitted,

Coordinating Committee
of the
Committee on the Care
of the Diabetic

By:

/s/ Robert F. Bradley, M.D.
Robert F. Bradley, M.D.
Medical Director
Joslin Clinic
Boston, Massachusetts

/s/ Henry Dolger, M.D.
Henry Dolger, M.D.
Professor of Clinical Medicine
Mount Sinai School of Medicine
City University of New York
New York, New York 10029

/s/ Peter H. Forsham, M.D.
Chief of Endocrinology
Professor, Department of Medicine
University of California Medical Center
San Francisco, California 94122

/s/ Holbrooke S. Seltzer, M.D.
Holbrooke S. Seltzer, M.D.
Chief of Endocrinology
Professor of Internal Medicine
Veterans Administration Hospital
University of Texas
Southwestern Medical School
Dallas, Texas 75235

/s/ Neil L. Chayet, Esq.
Neil L. Chayet, Esq.
Attorney for the Committee
15 Court Square
Boston, Massachusetts 02108

EXHIBIT B

UNITED STATES COURT OF APPEALS
FOR THE FIRST CIRCUIT

No. 73-1014

Robert F. Bradley, et al.,
Plaintiffs, Appellees,

v.

Caspar W. Weinberger, Secretary of
Health, Education and Welfare, et al.,
Defendants, Appellants.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

Before Coffin, *Chief Judge,*
Aldrich and McEntee, *Circuit Judges.*

William A. Brown, Assistant United States Attorney, with whom *James N. Gabriel,* United States Attorney, *Thomas E. Kauper,* Assistant Attorney General, Anti-Trust Division, *George Edelstein,* Attorney, Department of Justice, *Peter Barton Hunt,* Assistant General Counsel, *Joanne S. Sisik,* Chief, Appellate and Special proceedings Branch, and *Arthur N. Levine,* Attorney, Food, Drugs and Product Safety Division, were on brief, for appellant.

Neil L. Chayet, with whom *Harvey W. Freishtat* and *Chayet* and *Sonnenreich* were on brief for Robert F. Bradley, et al, plaintiffs, appellees.

July 31, 1973

Coffin, *Chief Judge.* Plaintiffs, 178 physicians who treat diabetes and one diabetes patient who use oral hypoglycemic agents to control the disease by lowering the blood sugar level, brought suit to enjoin the defendants Secretary of

Health, Education and Welfare and the Commissioner of the Food and Drug Administration (FDA) from enforcing and the defendant drug companies from complying with the FDA's proposal for altering the labeling of those drugs. The district court granted a preliminary injunction, being persuaded that there was a reasonable likelihood of success in showing that the FDA had failed to comply with the statutes and its own regulation requiring that under some circumstances labeling make reference to the existence of a serious medical controversy. We vacate the injunction for reasons important to the proper judicial role in reviewing administrative actions.

This controversy revolves around a long-term, federally funded study undertaken by the University Group Diabetes Program (hereafter the UGDP study) to determine the effects of oral hypoglycemic agents on vascular complications in patients with adult-onset diabetes. The study, involving twelve clinics and 1200 patients, consisted of four treatment groups: diet alone, diet plus regular insulin doses, diet plus varying insulin doses and diet plus fixed doses of either tolbutamide or phenformin (two hypoglycemic agents). After monitoring the patients for from five to eight years, the study concluded that the combination of diet and either tolbutamide or phenformin was no more effective than diet alone in prolonging life but that those oral agents might be more hazardous than diet or diet plus insulin insofar as cardiovascular mortality was concerned. The latter conclusion, which led the investigators to discontinue use of the agents in the study as an unethical risk, was based on findings that patients treated with the two agents used in the study suffered more than twice as many cardiovascular deaths and patients receiving the other treatments.

After the study received much publicity and criticism, the FDA convened an ad hoc committee of experts on May 21, 1970 to evaluate the study's findings and the following

day issued a press release agreeing with the UGDP study's conclusions and indicating that the agency would require labeling changes to reflect those views. After more extensive evaluation, the FDA concluded that protection of the public required a strong warning to physicians recommending use of an oral agent only if other treatments were inadvisable and noting that UGDP's findings regarding the apparently increased danger of cardiovascular mortality. This evaluation and proposed labeling change was first formally published in the FDA *Drug Bulletin* of June, 1971.

On October 7, 1971, the Committee on the Care of the Diabetic, consisting of eminent doctors and experts in the field including some of the plaintiff doctors, submitted through its counsel a petition to the FDA. It asked the FDA to rescind its labeling recommendation, insure that all future FDA comments on the UGDP study include references to its alleged deficiencies and controversial nature, provide petitioners with the complete raw data of the study, and, "in accord with its policy of fair balance", disseminate with equal emphasis and frequency studies and individual expert opinions differing with the study. The petition was accompanied by a detailed scientific critique of the UGDP study and some 250 pages of scentific studies, papers and comments illustrating the nature and extent of the opposition viewpoint. The study was primarily criticized for inadequate patient selection controls and use of fixed, rather than variable, doses of the drugs, contrary to allegedly accepted medical practice. The FDA proposal was attacked for extending the study's findings to all oral agents and patients despite the study's own warning that such extrapolation could not be made on a statistical basis. The petition also referred to two smaller studies which indicated no cardiovascular complications from oral agents. It was supplemented in January, 1972, by another 220 pages of scientific materials.

In the May, 1972, *Drug Bulletin*, the FDA published the "Final Labeling Approved For Oral Hypoglycemic Drugs", which proposed changes in the "indications" section of the label and the addition of a "special warning" section. The proposal speaks of "the increased cardiovascular hazard which appears to be associated with oral hypoglycemic agents", notes that the UGDP study was the basis for the change, recites its findings, states that these conclusions apply to all oral agents, not just those employed in the study, and ends with the comment that "Further studies are being undertaken to shed additional light on the role" of the oral agents. On June 5, 1972, the Commissioner formally replied to the Committee's position with an eleven-page, single-space letter addressing generally the legal and medical issues and with a 100 page appendix dealing specifically with the scientific criticisms of the study, criticizing the two contrary studies referred to by the petition, and appending the comments of major medical groups and various scientific papers supportive of the FDA's position. The Committee's counsel responded on July 13 with a four-page letter suggesting that the FDA's label might constitute misbranding in violation of two cited statutes, that this was one of the "rare cases" suggested by the Commissioner in which "substantial evidence" exists on both sides of an issue, making appropriate reflection of the controversy in the package insert. Counsel requested a formal evidentiary hearing, a stay of any further action pending final resolution, and the full patient records from the study. The Commissioner's response of August 3 stated that the petitioners were not entitled to a hearing and that only clinical studies were substantial evidence of drug effectiveness. He concluded by saying that, "we do not contend that you do not have standing either to prosecute your petition [sic] or to pursue an appeal to the courts" and that his two letters consituted final agency action reviewable by the courts pursuant to the Administrative Procedure Act.

This suit was filed on August 11, 1972 and a temporary restraining order issued that day. After a hearing and submission of affidavits of experts by both sides, the emergency district judge denied the preliminary injunction on August 30, finding that whatever irreparable injury might be suffered by the plaintiffs did not outweigh that suffered by the public represented by the defendants and that the plaintiffs had not demonstrated "a reasonable probability" of showing that the FDA's decision to require the warning was arbitrary or capricious. A second motion for a preliminary injunction was denied on September 21 by the judge to whom the case was permanently assigned because no new evidence or amendment of the complaint had been presented.

On October 17, 1972, the litigation entered an entirely new phase. On that date, plaintiffs filed a motion for leave to amend their complaint, supported by 13 affidavits by diabetes experts attesting to the controversy over the UGDP study, and new motions for a temporary restraining order and a preliminary injunction. The motions presented for the first time the argument that the FDA's proposed label was itself misleading and thus rendered the drug misbranded in violation of the statute, because it failed to reveal the existence of a "material weight of contrary opinion" among "experts qualified by scientific training and experience" as allegedly required by the agency's own regulation, 21 C.F.R. § 1.3. After oral argument, at which plaintiffs' counsel admitted this was an unprecedented case, being brought by the doctors and seeking to apply that regulation to the agency's own labeling recommendation, the district court in a Memorandum and Order granted on November 3, 1972, the motions to amend the complaint and for a preliminary injunction. It noted that "The application for preliminary injunction was heard on the affidavits filed by plaintiffs and defendants, and their arguments both oral and written" and stated that "the court is satisfied plaintiffs have

made a showing that there is reasonable likelihood upon a full hearing on the merits they would be successful in establishing the defendants . . . have not in the order described in the May 1972 Bulletin complied with 21 C.F.R. § 1.3.; 21 U.S.C. § 321(n) and 21 U.S.C. § 352(a).", and that "there is [absent an injunction] a likelihood of irreparable injury to the plaintiffs" greater than would be visited upon the defendants by such relief.

The district court had jurisdiction to review the administrative action under the Administrative Procedure Act (APA), 5 U.S.C. § 704, because it was "final agency action for which there is no other adequate remedy in a court." *See Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967); *Weinberger* v. *Hynson, Wescott & Dunning, Inc.*, 41 U.S. L.W. 4848, 4853 (U.S. June 18, 1973).[1] There is no dispute

[1] The right to petition the court of appeals for review under 21 U.S.C. § 355(h) is available only to a drug-marketing applicant after an order refusing or withdrawing approval of a drug application. Although the FDA has no direct statutory power to compel labeling changes, it may refuse or withdraw approval of an application, under § 355(d) or (e), if new information demonstrates that the labeling is "false or misleading." Since the drug companies here were willing to amend their labels in accordance with the FDA proposal, no withdrawal procedures were ever begun and thus the agency action was final in a meaningful sense. *Abbott, supra.*

Before this court, the government, for the first time, argued that plaintiffs did not have standing to sue, not being persons "adversely affected or aggrieved by agency action within the meaning of a relevant statute" as required by 5 U.S.C. § 702. Even assuming that the government may still raise this claim notwithstanding an explicit concession of standing by the specialized agency charged with interpretation and enforcement of the relevant statute, the case is properly before us. While there might be some doubt whether the plaintiff doctors, who clearly alleged "injury in fact", *Sierra Club* v. *Morton*, 405 U.S. 727 (1972); *United States* v. *Students Challenging Regulatory Agency Procedures*, 41 U.S.L.W. 4866 (U.S. June 18, 1973), because of the impact of the label changes on their

over the scope of review—whether the agency action was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).[2] The action challenged was informal agency action, subject to judicial review under that standard.[3] *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402 (1971); *Camp* v. *Pitts*, 41 U.S.L.W. 3515 (U.S. Mar. 26, 1973).

Significantly, there is also no controversy over the basis for judicial review—"the full administrative record that was before the [Commissioner] at the time he made his decision." *Overton Park, supra*, 401 U.S. at 420.[4] Yet, as

medical practice and on malpractice suits, have an interest "arguably within the zone of interests to be protected or regulated", *Data Processing Service* v. *Camp*, 397 U.S. 150 (1969), there can be no question that the plaintiff patient's interest is in the very center of that zone.

[2] While the plaintiffs now also contend that the agency's failure to follow its own regulations is a violation of due process, thus apparently also invoking the review standard of § 706(2)(B), "contrary to constitutional right, power, privilege, or immunity", that approach would change neither the nature of the review nor the result. If an agency action violates a regulation, it is "not in accordance with law" as well as violative of due process, *United States* v. *Griglio*, 467 F.2d 572 (1st Cir. 1972). Moreover, courts must review agency actions under both standards in all cases. *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402, 414 (1971). If, however, a regulation has been violated, there would seldom be occasion to decide the constitutional issue.

[3] Plaintiffs do not now claim that they are entitled to an evidentiary administrative hearing.

[4] The plaintiffs insist that the record must include not only their petition and the Commissioner's response, which the record before us contains, but also the original patient records of the UGDP study, any intra-agency and other memoranda, factual reports and scientific studies before the Commissioner, and the minutes taken during the deliberations of the ad hoc advisory committee convened by the FDA the day before its first press release regarding the study. While in light of our discussion we need not resolve the

the district court's brief memorandum indicates, the preliminary injunction was based not on a review of that record but on the affidavits presented by both sides to the court. As the Supreme Court has only recently reiterated, "the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court." *Camp* v. *Pitts, supra,* 41 U.S.L.W. at 3515. There are strong policy reasons behind this requirement. Litigation affidavits are often "merely *'post hoc'* rationalizations . . . which have traditionally been found to be an inadequate basis for review." *Overton Park, supra,* 401 U.S. at 419; *see Trailways of New England, Inc.* v. *C.A.B.,* 412 F.2d 926, 931 (1st Cir. 1969). Moreover, this rule is significant in limiting courts to their proper role. Courts are to determine whether an agency's action was arbitrary or capricious in light of the information it confronted. It is a re-view, a second look at the same material, not a re-doing. And, of course, limiting review to the existing administrative record also saves judicial time.

The requirement that review be on the administrative record parallels and supports the exhaustion of administrative remedies doctrine which reflects similar policies. To the extent that the record reflects consideration of arguments made and evidence submitted, it also reflects the focus which the agency had in bringing to bear its expertise. The exhaustion requirement, as it applies to administrative agencies, is no mere technical rule to enable courts to avoid difficult decisions. It is grounded in substantial

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propriety of each of these requests, we reiterate what we recently stated in an analogous situation: "We think the law requires production of the entire administrative record . . . . While there may be some instances in which the entire record need not be filed, where the correctness of factual findings are involved or where the complainants request the full record, we think the agency must produce it in court. *Cf.* 28 U.S.C. § 2112(b)." *Silva* v. *Romney,* No. 73-1200 (1st Cir. July 5, 1973) (slip op. at 3 & n. 1).

concerns not only of fairness and orderly procedure, *N.L.R.B.* v. *Rexall Chemical Co.,* 370 F.2d 363, 365-66 (1st Cir. 1967); *United States* v. *Tucker Truck Lines, Inc.,* 344 U.S. 33, 36-37 (1952), but also of competence. Courts are not best equipped, as both sides here readily agree, to judge the merits of the scientific studies and the objections to them. Specialized agencies like the FDA are created to serve that function. In this case, the regulation which, in their motion to amend, plaintiffs contend specifically governs the content of a balanced label, 21 C.F.R. § 1.3, was never presented to the Commissioner nor referred to in the administrative record. It is the significance of this omission that governs our disposition.

Plaintiffs argue that while this regulation was never mentioned in the administrative proceedings, the concept of "fair balance" which it represents was fully presented and argued by them in their initial petition, was explicitly rejected by the Commissioner in his initial letter, and that the specific statutes under which this regulation was promulgated were mentioned in plaintiffs' letter of response. While we recognize that the concept was put forward, are fully aware of the disadvantages of further delay, and do not wish to render the exhaustion doctrine a rigid and technical barrier, several factors in this case lead us to insist that the specific argument now pressed be first thrashed out in the administrative arena.

Most significantly, this is an unprecedented argument. As plaintiffs' counsel readily admitted in oral argument before the district court, there appears to be no prior case in which an FDA drug labeling decision was challenged not by the producer but by concerned medical practitioners, and no case in which the misbranding statutes and regulations were sought to be applied not to the manufacturer's label but to the FDA's proposal for alteration of the label in light of new information. It is thus not surprising that the dialogue that did occur regarding "fair balance" was

on an entirely different plane. The Food, Drug and Cosmetic Act as amended in 1962 requires that applicants seeking approval for markting of new drugs present "substantial evidence" of the drug's effectiveness as well as evidence of its safety. The term "substantial evidence" is defined in the statute to mean "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved". 21 U.S.C. § 355(d). The FDA has promulgated a detailed regulation to further refine and clarify that definition. 21 C.F.R. § 130.12. *See Hynson, supra.* Yet the statute provides that approval of an application may be refused or withdrawn not only because "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have", 21 U.S.C. §§ 355(d)(5), (e)(3), or there is "insufficient information to determine whether such drug is safe", § 355 (d)(4), *see also* § 355(e)(2), but also if "based on a fair evaluation of all material facts", the drug's labeling is "false or misleading in any particular." §§ 355(d)(6), e(4) (second sentence).

The Commissioner, in his ruling on plaintiffs' petition, rejected the argument for "fair balance" because he said that Congress had determined in 1962 that "unsubstantiated expert opinion could no longer suffice to establish the effectiveness of drugs", and that "Except perhaps in rare instances where there is substantial evidence on both sides of an issue, therefore, it is inappropriate to utilize the package insert to present all aspects of the evidence relating to safety and effectiveness." Since he found that not the situation here, he saw "no basis" for a balanced label. Plaintiffs' reply, although noting the possibility that the FDA's proposal might constitute misbranding under the relevant statutes, *see infra,* primarily argued that "this is in fact one of those rare instances" in which "substantial evidence" exists on both sides of an issue and thus, as the Commissioner's letter suggested, warranted balanced labeling treatment. The Commissioner's reply was that the plaintiffs had

not in fact presented "substantial evidence" as defined by Congress.

Now, aware of the stringency of the substantial evidence test, *see Hynson, supra,* the plaintiffs argue that the misbranding statutes and regulation apply. Section 502 of the statute, 21 U.S.C. § 352, declares that "A drug . . . shall be deemed to be misbranded—(a) if its labeling is false or misleading in any particular." The definitional statute (21 U.S.C. § 321(n)) provides: "If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading, there shall be taken into account (among other things) not only representations made or suggested . . . but also the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates." Implementing the latter definition is regulation 1.3:

> "The existence of a difference of opinion, among experts qualified by scientific training and experience, as to the truth of a representation made or suggested in the labeling is a fact (among other facts) the failure to reveal which may render the labeling misleading, if there is a material weight of opinion contrary to such representation."

One reading of this regulaton would suggest that unsubstantiated individual clinical opinions of qualified experts, which are insufficient under the "substantial evidence" test enacted in the effectiveness section, might be sufficient to create a fact omission of which might render the labeling misleading.

The Commissioner never considered the meaning of this regulation, its relationship to the substantial evidence test, the intersection of the safety, effectiveness, and misbranding requirements, or the applicability of the misbranding requirements, both statutory and regulatory, to an FDA

proposal for re-labeling, for the simple reason that the issue was not presented to him.[5] Arguably these are simply issues of law which we are fully capable of resolving without administrative assistance. But as the Supreme Court has very recently noted in similarly resolving a closely analogous case, the interpretation of even definitional sections in the drug law will often involve expert knowledge and the ability to evaluate the scientific evidence that becomes relevant. *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 41 U.S.L.W. 4858, 4860-61 (U.S. June 18, 1973). Moreover, we have here not only novel issues concerning the interpretation of the statute, which the specialized enforcement agency should first undertake, but also unprecedented inquiries as to the meaning of the agency's own regulations. It is thus no answer to say that an agency need not be reminded of its own regulations. Finally, both the definitional statute and its implementing regulation on which the district court relied explicitly anticipate the exercise of administrative discretion, since they require only that the omission of expert differences of opinion be considered, along with all other relevant facts, in determining whether a label is misleading. As the Court recently reaffirmed: "uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure." *Bentex, supra* at 4861.

An equally important reason for insisting on exhaustion here is that insofar as the record reveals the administrative

[5] Similarly he never considered the applicability or meaning of 21 C.F.R. § 1.106(b)(3)(i), which plaintiffs refer to as the "full disclosure" regulation, but which they failed to disclose not only to the Commissioner but to the district court. Obviously, the relevance and impact of that regulation should also first be presented for administrative consideration.

process seems to have been working well in this instance. The initial ad hoc advisory committee convened by the agency included several eminent critics of the UGDP study, indeed some of the plaintiffs here. While the response to Dr. Bradley's initial communications may not have been fully satisfactory, the response to the Committee's petition was both lengthy, detailed, and technical. Even the rebuttal letter, essentially in the form of a petition for reconsideration, a useful procedure in insuring that objections to even the supposedly final agency decision are first brought to its attention, received a specific and complete response. Arguments, studies, and materials, were not ignored; difficult problems were not swept under the rug. The communications evidenced agency recognition of the plaintiffs' expert status, and, as the concession of standing indicates, receptivity to criticism. Additionally, we were informed at oral argument that extensive negotiations between the parties to arrive at a mutually acceptable solution to the labeling problem had been carried on during much of this litigation. We thus have more than a pious hope that a remand to the agency will not only not be futile, but could well produce the most informed and responsible solution possible.

Because the plaintiffs failed to exhaust their administrative remedies regarding the issues they now present and, consequently, the district court reviewed the agency decision on something other than the administrative record, we must vacate the injunction.[6]

Injunction vacated; case remanded for further proceedings consistent with this opinion.

[6] We therefore need not decide whether reversal would have been required, as argued by the defendants, because the district court, in granting the injunction, did not, as required by Fed. R. Civ. P. 52(a), "set forth the findings of fact and conclusions of law which constitute the grounds of its action". While the context will often render obvious the grounds of decision, district courts should generally follow the rule's mandate to obviate any possibility of misunderstanding, unnecessary reversal and/or delay.

EXHIBIT C

WESTERN UNION MAILGRAM

CHAYET AND SONNENREICH
6 FAYETTE ST
BOSTON MA 02109

RECEIVED OCT. 16, 1974, NEIL L. CHAYET

THIS MAILGRAM IS A CONFIRMATION OF THE FOLLOWING MESSAGE:

6173570204 TDHT BOSTON MA 82 10-15 0710P EDT

PHS G DONNALD WHEEDON DIRECTOR MEGABOLIC SERVICES NATIONAL INSTITUTE OF HEALTH,FONE: DLR
BETHESDA MD

HAS BEEN INFORMED THAT A DRAFT BIOMETRIC STUDY IS AVAILABLE AND HAS BEEN CIRCULATED FOR REVIEW AND COMMENT. I AM REQUESTING COPY OF THIS REPORT BE IMMEDIATELY MADE AVAILABLE TO REPRESENTATIVE OF THE COMMITTEE AND THE CARE OF THE DIABETIC. ALSO REQUEST THAT ACCESS TO THE RAW DATA WHICH WAS ACCORDED TO THE BIOMETRIC STUDY BE SIMILARLY AND IMMEDIATELY MADE AVAILABLE TO REPRESENTATIVE OF THE COMMITTEE AND THE CARE OF THE DIABETIC. YOUR URGENT REPLY TO THIS REQUEST IS AWAITED.

NEIL L CHAYET COUNSEL AND SONNENREICH 6 FAYETTE ST BOSTON MA

19:10 EDT

HGHBSNT HSB

EXHIBIT D

WESTERN UNION TELEGRAM

BBD221(1443)(1-0238180291)PD 10/18/74 1441

TLX HEWNIH BHDA C

ZCZC 1 NL PD BETHESDA MD OCT 18

PMS NEIL L CHAYET COUNSEL

CHAYET AND SONNENREICH

6 FAYETTE STREET

BOSTON MASSACHUSETTS 02116

RECEIVED OCT. 23, 1974,
CHAYET AND SONNENREICH, P.C.

PRELIMINARY DRAFT OF REPORT OF BIOMETRICS SOCIETY HAS BEEN PROVIDED TO ME FOR MY INFORMATION AS HEAD OF THE CONTRACTING AGENCY FOR THIS REPORT AND HAS NEVER BEEN CIRCULATED FOR REVIEW AND COMMENT. FINAL DRAFT WILL NOT BE CIRCULATED FOR REVIEW AND COMMENT BUT WILL BE PUBLISHED IN THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION.

DR G DONALD WHEDON, DIRECTOR

NIAMDD NIH

EXHIBIT E

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

Watergate 600, Suite 720
600 New Hampshire Avenue, Northwest
Washington, D.C. 20037

(202) 965-4150

November 4, 1974

Mr. Peter Hutt
Assistant General Counsel
Food and Drug Division
Food and Drug Administration
Department of Health, Education and Welfare
Office of the Secretary
5600 Fishers Lane
Rockville, Maryland 20852

Dear Peter:

Enclosed you will see the telegram I sent to Dr. G. Donald Wheeden on October 15, 1974 and his reply to me of October 21, 1974. You will note that the reply is not responsive to the request I made.

Since the Biometric Society study has been circulated for review and comment, I thought it only fair that the Committee for the Care of the Diabetic be allowed to see such study and to comment upon it. I also feel it is essential that the Committee have available the raw data which was given to the Biometric Society so that we might see the basis upon which the study founded its conclusions and recommendations.

I wish to formally make the request, on behalf of the Committee, for both a copy of the currently circulated draft and for access to the raw data upon which the draft was

based. It is my belief that this material is lawfully available to the Committee as an interested party under the Freedom of Information Act and on the basis that these documents and data have been circulated to other interested persons for review and comment.

I look forward to your early reply on this most urgent matter.

Yours truly,

/s/ Neil L. Chayet
Neil L. Chayet

EXHIBIT F

Attachment 5

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Rockville, Md. 20852

November 11, 1974

Received Nov. 15, 1974, Chayet and Sonnenreich, P.C.

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
Six Fayette Street
Boston, Massachusetts 02116

Dear Mr. Chayet:

This is in response to your letter of November 4, 1974, requesting a copy of the current draft of the Biometric Society and access to the raw data given to the Society upon which the Society has drafted its conclusions and recommendations.

This is to advise you that the Food and Drug Administration does not have a copy of a draft report, and we have no information whatever about it being circulated for review and comment. As I have previously advised you, both the UGDP study and the Biometric Society study were funded by NIH, not by FDA, and we have had no connection with the report or the material sent to the Biometric Society committee for their review.

I am forwarding your letter to Sidney Edelman, Esq., Assistant General Counsel for the Public Health Division

and thus for NIH, with the request that he pursue the matter further.

Sincerely yours,

/s/ Peter Barton Hutt
Peter Barton Hutt
Assistant General Counsel
Food and Drug Division

cc: Sidney Edelman, Esq.

EXHIBIT G

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Washington, D.C. 20201

November 22, 1974

Received Nov. 25, 1974, Chayet and Sonnenreich, P.C.

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
Six Fayette Street
Boston, Massachusetts 02116

Dear Mr. Chayet:

Reference is made to your letter of November 4, 1974 requesting a copy of a draft Biometric Society study and the raw data on which the study was based.

Inasmuch as any such materials would be in the files of the National Institute of Arthritis, Metabolism, and Digestive Diseases, we have referred your letter to that Institute for reply.

Sincerely yours,

/s/ SIDNEY EDELMAN
Sidney Edelman
Assistant General Counsel
for Public Health

EXHIBIT H

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Washington, D.C. 20201

December 3, 1974

Received Dec. 6, 1974, Chayet and Sonnenreich, P.C.

Mr. Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
Six Fayette Street
Boston, Massachusetts 02116

Dear Mr. Chayet:

Further reference is made to the exchange of telegrams between you and Dr. G. Donald Wheden, Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH, and correspondence dated November 4 and 11 between you and Mr. Peter Barton Hutt, Assistant General Counsel, Food and Drug Division, FDA. Your request was referred to me because of my responsibilities under the Freedom of Information Act.

In your letter and telegram you asked for a draft of a report of a review by the Biometrics Society of a long term study of the safety and effectiveness of oral drugs in diabetes. The Biometrics Society review was contracted for by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

The Department's policy calls for the fullest possible disclosure of records consistent with the requirements of administrative necessities and confidentiality recognized by the Freedom of Information Act. Copies of the Act (5

U.S.C. 552) and the Department's implementing Public Information Regulation (45 CFR, Part 5) are enclosed for your information. Included in records available section 5.72 (e), you will note: "The final report of a grantee or a contractor of the performance under any research, development, or demonstration project records, other than reports, produced in such projects, such as films, computer software, other copyrightable material and reports of inventions, will be available, except that considerations relating to obtaining copyright and patent protection may require delay in disclosure for such period as necessary to accomplish such protection.

The material you cite is a preliminary draft, not a final report. Once the final report is completed, the National Institute for Arthritis, Metabolism, and Digestive Diseases will be glad to furnish it promptly to you.

You have the right to appeal this decision within thirty (30) days. Should you wish to do so, the procedure is outlined under Subpart G of the Department's Regulation. Any such appeal should be addressed to the Assistant Secretary for Health, Department of Health, Education, and Welfare, 330 Independence Avenue, S.W., Washington, D.C. 20201.

Sincerely yours,

/s/ Russell M. Roberts
Russell M. Roberts
Freedom of Information Officer
Office of Public Affairs

Enclosure

EXHIBIT I

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

January 2, 1975

Dr. Charles C. Edwards
Assistant Secretary for Health
Department of Health, Education, and Welfare
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Edwards:

This is to request review of the denial on December 3, 1974 of my requests on behalf of the Committee on the Care of the Diabetic (CCD) for a copy of the draft of the Biometrics Society report on the University Group Diabetes Program (UGDP) and for access to the raw data on which the report is based (Attachment 1).

These materials were earlier requested through an exchange of telegrams with Dr. G. Donald Whedon, Director of the National Institutes of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, in October 1974 (Attachments 2 and 3) and an exchange of correspondence with Mr. Peter Barton Hutt, Assistant General Counsel, Food and Drug Division, Food and Drug Administration, in November 1974 (Attachments 4 and 5).

The basis for the request is my belief that such materials constitute "identifiable records" of an agency lawfully available to the public under the Freedom of Information Act (5 USC § 552). In establishing a general policy of disclosure rather than secrecy, the FOIA requires government

agencies to make available to the public a broad range of information that is not specifically exempted, with the burden of justifying non-disclosure placed on the agency and with any cited exemption to be narrowly viewed.

Neither the letter of December 3 nor any FOIA law or regulation restricts CCD's access to the raw data on which the UGDP and the Biometrics studies are based. Accordingly, CCD assumes that access to such data is to be provided.

With respect to the Biometrics study, the denial of December 3 was purportedly based on 45 CFR § 5.72(e) of DHEW's Public Information Regulation. However, as a part of the "records available" section of the Regulation, Section 5.72(e) simply affirms public access to the "final report of a grantee or a contractor . . . under any research . . . project" with certain exceptions not relevant here. Neither 5.72(e) nor any other section of the Regulation discusses, much less restricts, the availability of identifiable records which are not yet "final reports". DHEW's denial is, therefore, apparently premised on a notion that the public can have access only to what is specifically allowed, whereas the FOIA guarantees disclosure of all records not specifically prohibited (5 USC § 552(c)).

Of the nine specific legislative exemptions to full disclosure, however, the only exemption that could even conceivably be invoked to justify the denial of the requested Biometrics study is the fifth

> inter-agency or intra-agency memorandums or letters which would not be available by law to a party other than an agency in litigation with the agency (§ 552 (b)(5)).

In establishing Exemption 5, Congress expressly intended "to delimit the exception as narrowly as consistent with efficient Government operation." S. Rep. No. 813, p. 9. The Exemption has been generally construed to permit government non-disclosure only to the extent necessary to protect

materials reflecting policy-making processes as opposed to factual or investigatory reports. In *Bristol Myers Co.* v. *FTC* 424 F. 2d 935, cert. denied 400 U.S. S24 (1970), the distinction was explained as follows:

> Purely factual reports and scientific studies cannot be cloaked in secrecy by an exemption designed to protect only "those internal working papers in which opinions are expressed and policies formula and recommended" at 939 quoting *Ackerly* v. *Ley*, 420 F. 2d 1336, 1341 (1969)).

The Biometrics study, conducted over the past 18 months by a special panel of the Society at a cost of $80,000, has been charged to investigate the systems of data evaluation adopted by the UGDP and to determine their acceptability according to objective biostatistical standards. The panel was not intended to delve into the realm of policy; rather, its report was to provide the purely factual predicate upon which DHEW policy could then be made.

DHEW's promulgation of 5.72(e) attests to the limited scope of Exemption 5 by guaranteeing disclosure of the final report of the Biometrics study. It is all the more unclear, therefore, why a preliminary report of the same study, acknowledged to be in DHEW's possession, should be regarded any differently for purposes of disclosure.

In addition to the FOIA-guaranteed public interest in disclosure, CCD has a particularized interest in disclosure of the documents requested herein. Consisting of approximately 180 eminent diabetologists from around the country, CCD was organized to ensure that any policy-making based on the UGDP study was informed by a broader spectrum of medical and scientific evidence and opinion. It was when FDA indicated its intention to act solely on the basis of the UGDP study and without providing access to the data on which the findings were based that CCD sought the assistance of the Court. *Bradley* v. *Weinberger* 483 F.2d 410 (1st Cir. 1973).

Particularly relevant for purposes of the request herein is the First Circuit's view of the type of information to which CCD is entitled:

> The plaintiffs (CCD) insist that the record must include not only their petition and the Commissioner's response, which the record before us contains, *but also* the *original patient records of the UGDP study, any intra-agency and other memoranda, factual reports and scientific studies before the Commissioner* and the minutes taken during the deliberations of the ad hoc advisory committee convened by the FDA the day before its first press release regarding the study. While in light of our discussion we need not resolve the propriety of each of these requests, we reiterate what we recently stated in an analogous situation: "We think the law requires production of the entire administrative record . . . While there may be some instances in which the entire record need not be filed where the correctness of factual findings are involved or where the complainants request the full record, we think the agency must produce it in court. [citing cases.] (483 F. 2d 410, at fn. 4) (emphasis supplied).

The First Circuit has thus implicitly reaffirmed the discoverability of the information CCD is requesting. In fact, it was in the hope of full dialogue and disclosure at the administrative level that the Court remanded the matter for additional agency consideration.

In my judgment, denial of the request herein would, therefore, violate not only the provisions of the FOIA but also the express intent of the Court.

Very truly yours,

Neil L. Chayet

Enclosures

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Washington, D.C. 20201

Received Jan. 17, 1975, Chayet and Sonnenreich, P.C.

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
Watergate 600, Suite 720
600 New Hampshire Avenue N.W.
Washington, D.C. 20037

Dear Mr. Chayet:

Thank you for your letter of January 7 in which you ask for a review of the denial of your request for a copy of a report of the Biometrics Society on the University Group Diabetes Program.

The facts of this case are currently being reviewed in my office, and I will inform you of the results of my decision in the near future.

Sincerely yours,

/s/ CHARLES C. EDWARDS
Charles C. Edwards, M.D.
Assistant Secretary for Health

EXHIBIT J

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE OF HEALTH
BETHESDA, MARYLAND 20014

Building 31 Pages 9A 52
Area Code 301-496-5877

January 27, 1975

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
Watergate 600, Suite 220
629 New Hampshire Avenue, N.W.
Washington, D.C. 20037

Dear Mr. Chayet:

In response to your request transmitted to me recently by Dr. Charles C. Edwards, I am making available to you a copy of the report of the Biometric Society on the University Group Diabetes Program. To my knowledge, no one in the Department of Health, Education and Welfare has ever had any of the raw data of the UGDP study.

Sincerely yours,

/s/ G. DONALD WHEDON, M.D.
G. Donald Whedon, M.D.
Director
National Institutes of Arthritis,
Metabolism, and Digestive Diseases

Enclosure

EXHIBIT K

CHAYET AND SONNENREICH, P. C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

May 6, 1975

Theodore Cooper, M.D.
Acting Assistant Secretary for Health
Department of Health, Education and Welfare
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Cooper:

This is to renew my appeal of January 7, 1975 from the denial of my requests on behalf of the Committee on the Care of the Diabetic (CCD) for a copy of the draft of the Biometrics Society report on the University Group Diabetics Program (UGDP) and for access to the raw data on which the report is based.

The letter from Dr. Edwards of January 17 was not responsive to my request relative to the raw data.

The response of Dr. G. Donald Whedon on January 27 was similarly unresponsive in that it did not provide the requested preliminary draft of the Biometrics Society report, but rather produced only the galley proofs of the final version as eventually published in the Journal of the American Medical Association. Further, Dr. Whedon did not respond to my request that the CCD be accorded full access to the UGDP raw data or, at the very least, the same access as was accorded the Biometrics Society.

Your review of the denial of the foregoing requests is again requested in accordance with the provisions of the Freedom of Information Act (5 USC § 552) and DHEW's implementing regulations (45 CFR Part 5) as a final attempt to secure relief at the administrative level.

The CCD also requests that the following be made available: The UGDP study research design and protocol submitted with the funded initial grant application, as well as any research designs and protocols submitted with application for continuation, renewal or supplemental grants (including interim progress reports) whether funded or not. In addition, the CCD requests a full statement detailing all budgets, appropriations, actual allocations and expenditures with respect to the UGDP study. This information is sought pursuant to DHEW's regulation with respect to research designs and protocols published in the Federal Register of May 1, 1975 (40 F.R. 18997).

This letter renewing my earlier request is a final attempt to achieve an administrative resolution of this matter.

Very truly yours,

Neil L. Chayet

NLC:jlp

EXHIBIT L

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Washington, D.C. 20201

May 23, 1975

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
6 Fayette Street
Boston, Massachusetts 02116

Dear Mr. Chayet:

Thank you for your letter of May 6 regarding your request for further information in the Biometrics Society report on the University Group Diabetes Program.

I have reviewed this matter and find that Dr. Whedon did respond to your request regarding the raw data on which the UGDP study was based. In his letter of January 27, Dr. Whedon stated that this Department does not now have and never has had any of the raw data on which the UGDP study was based. Given that the data you request are not records belonging to this Department, I have no Freedom of Information Act jurisdiction over them.

Your other previous request was for the draft report of the study. The only draft report which the Department received was the one provided to you, viz. the galley proofs. We have no other drafts.

Your request for the UGDP study research design and protocol is a new request. I have, therefore, transmitted it to the National Institutes of Health for direct reply.

Should you have further questions regarding this matter, please do not hesitate to contact my office.

Sincerely yours,

/s/ THEODORE COOPER, M.D.
Theodore Cooper, M.D.
Acting Assistant Secretary for Health

EXHIBIT M

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

June 3, 1975

Dr. Theodore Cooper
Acting Assistant Secretary for Health
Department of Health, Education, and Welfare
330 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Cooper:

Thank you for your letter of May 23, 1975 regarding the law firm's request for information relating to the University Group Diabetes Program.

As you stated in your letter, Dr. Whedon did respond to me that he did not have in his physical possession the raw data upon which the UGDP study was based. However, I call to your attention the fact that this study was funded entirely by the National Institute of Health of the Department of Health, Education and Welfare, and unless a specific provision was written into the original contract authorizing this study, the materials collected, which would include computer tapes and other means of study, storage and analysis, are the property of the United States Government and therefore are constructively in the possession of the Government. Since such materials have been paid for with Federal funds, it is, in our judgment, entirely appropriate for the National Institutes of Health to request that such raw data be made available to us regardless of

where it is being kept and stored. It is our belief that the statement by Dr. Whedon that NIH does not have in its physical possession such data is begging the question; such data has been federally paid for and, under the Freedom of Information Act, should be available.

I would like it clearly understood that we are not concerned with breaching any confidentiality in terms of patient identity. We are making this request so that the basic materials upon which a scientific controversy has raged can be carefully reviewed and analyzed. It is our belief that such raw data does in fact "belong" to the Department of Health, Education, and Welfare and, upon your request to whoever is the custodian, it can be made available for such analysis.

With respect to our request for the UGDP study research design and protocol, we are appreciative of your transmitting our request to NIH. It is our belief that once we have in hand all materials requested, we will be able to be more completely informed about the basic foundation upon which any hypotheses have been drawn in the UGDP study.

Yours truly,

/s/ NEIL L. CHAYET
Neil L. Chayet

NLC/sjm

EXHIBIT N

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

July 8, 1975

Theodore Cooper, M.D.
Assistant Secretary for Health
Department of Health, Education, and Welfare
Public Health Service
Washington, D.C. 20201

Dear Dr. Cooper:

I am in receipt of your letter of June 24, 1975 responding to my formal request to you for the raw data relating to the University Group Diabetes Program study.

I am somewhat perplexed by your answer that such material not available to the Department of Health, Education, and Welfare, in light of the recently published Federal Register regulations relating to the oral hypoglycemic drugs (40 FR 28587 et seq.). I direct your attention to 40 FR 28589, where the Commissioner of the Food and Drug Administration states that a study was contracted, through the National Institute of Arthritis, Metabolism, and Digestive Diseases, to the Biometrics Society to do an in-depth assessment of the scientific quality of the UGDP study. It is obvious that such study has to examine the raw data and, in fact, the regulations state that the Biometrics Society ". . . made new analyses from the original data." (40 FR 28590). If such material was available to the Biometrics Society, fairness and evenhand-

edness would dictate that the Department of Health, Education, and Welfare would also see to it that such material is made available to the Committee on the Care of the Diabetic, especially in light of the preamble of Commissioner Schmidt in the proposed rules relating to oral hypoglycemics, where he recognizes the legitimacy of concern by the Committee on the Care of the Diabetic and the nature of the scientific controversy.

It is the hope of the CCD that this controversy can be resolved through scientific analysis rather than legal recourse. It is for this reason that I again respectfully request that the raw data that was made available to the Biometrics Society and which is the basis of the UGDP controversy be made available to the Committee on the Care of the Diabetic.

I look forward to an early reply to this request.

Yours truly,

/s/ NEIL L. CHAYET
Neil L. Chayet
Counsel
Committee on the Care of the Diabetic

EXHIBIT O

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

July 11, 1975

Mr. Linden F. Neff
Grants Management Officer
National Institute of Arthritis,
Metabolism and Digestive Diseases
5333 Westbard Avenue, Room 610
Bethesda, Maryland 20014

Dear Mr. Neff:

Thank you for the courtesy of meeting with me on July 7 relative to this law firm's request on behalf of the Committee on the Care of the Diabetic (CCD) for information concerning the UGDP study, research design and protocol and additional budgetary documents under the Freedom of Information Act (see letter of Neil L. Chayet, Esq. to Dr. Theodore Cooper of May 6, 1975).

In the course of my review of the documents which you provided, I requested that the following documents be photocopied and transmitted to our offices:

1. Monies awarded by NIAMDD to each institution participating in the UGDP study for each year of the study;
2. Return of Expenditures (ROEs) for each institution participating in the UGDP for each year of the study;

3. Progress Reports prepared by each institution and by the UGDP Coordinating Center for each year of the study;
4. All newsletters and minutes prepared by the Coordinating Center during the course of the study;
5. Original research design and protocols for each institution participating in the study;
6. Samples of all DHEW forms that have been used to certify institutional compliance with rules relative to protection of human subjects;
7. Assurances filed by each institution during the course of the study that informed consent from the patient had been secured, including actual informed consent forms;
8. Copies of all documentation in the file relative to the UGDP Coordinating Center;
9. Copies of all documentation in the file relative to the University of Maryland as a participating institution (Principal Investigator—Dr. Christian Klimt).

We agreed that photocopying of the above materials, with the exception of Items 8 and 9, would begin immediately and that the materials would be sent as soon as ready and hopefully within the next week. We further agreed that you would telephone me on July 14, 1975 to give me an estimate of the effort involved in reproducing Items 8 and 9.

In the course of our meeting, you informally indicated that you were not authorized to provide CCD with copies of summary statements submitted by peer groups reviewing the merits of the UGDP study as it has been conducted from 1960 to the present time. You further indicated that information relative to personnel salary would not be made

available. CCD hereby makes formal request for access to such information. In addition, CCD specifically reserves the right to request additional information under the Freedom of Information Act as it becomes aware of the existence of such information.

Once again, let me thank you for your courtesy and cooperation.

Very truly yours,

Harvey W. Freishtat

HWF/sjm

EXHIBIT P

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

OFFICE OF THE SECRETARY

WASHINGTON, D.C. 20201

July 30, 1975

Received July 31, 1975, Chayet and Sonnenreich, P.C.

Mr. Harvey W. Freishtat
Chayet and Sonnenreich, P.C.
6 Fayette Street
Boston, Massachusetts 02116

Dear Mr. Freishtat:

Reference is made to your letter dated July 11, 1975, addressed to Mr. Linden F. Neff, Grants Management Officer, National Institute of Arthritis, Metabolism, and Digestive Diseases. Your request has been forwarded to me because of my responsibilities under the Freedom of Information Act. The Department's policy is one of the fullest possible disclosure limited only by the obligations of confidentiality and the administrative necessities recognized by the Act. Copies of the FOI Act (5 U.S.C. 552) and the Department's implementing Public Information Regulation are enclosed and referred to below.

It is my understanding that in order for you to better define what you really wanted from the NIAMDD files, arrangements were made for you to visit the NIH on July 7, 1975, to review material relating to the UGDP Study. Subsequent to this meeting you requested copies of a more specific list of documents. It is our intention to release all of the information requested, except; (1) specific parts of each summary statement that reflect only opinions of the consultants serving as members of the initial review group and (2) salaries of individuals named in the applications. In the appendix of the Department's implementing Public Information Regulation (45 CFR Sec. 5.73) it is stated that summaries of recommendations of review groups (pink sheets) are generally not available. In addition, opinions in inter-agency or intra-agency memoranda or letters made by government officers, employers, or consultants may be denied in accordance with 5 U.S.C. 552(b)(5) of the Freedom of Information Act.

In view of the above, all opinions of the consultants serving as members of the initial review group will be deleted from the summary statements before they are released. Salaries of individuals named in the research grant applications are denied in accordance with 5 U.S.C. 552(b)(4) of the Freedom of Information Act and 45 CFR 5.71 of the Public Information Regulation, since disclosure would constitute a clearly unwarranted invasion of personal privacy.

You have the right to appeal this decision within thirty (30) days. Should you wish to do so, the procedure is outlined under Subpart G of the Department's Regulation. Any such appeals should be addressed to the Assistant Secretary for Health, Department of Health, Education, and Welfare, 330 Independence Avenue, S.W., Washington, D.C. 20201.

Sincerely yours,

/s/ RUSSELL M. ROBERTS
Russell M. Roberts
Freedom of Information Officer
Office of Public Affairs

Enclosure

EXHIBIT Q

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Washington, DC.. 20201

August 7, 1975

Neil L. Chayet, Esq.
Chayet and Sonnenreich, P.C.
6 Fayette Street
Boston, Massachusetts 02116

Dear Mr. Chayet:

In response to your additional request regarding the raw data relating to the University Group Diabetes Program study, I have made further extensive inquiries of both the National Institutes of Health and the Food and Drug Administration.

Neither agency has ever had the raw data in its possession. The FDA labeling recommendations were based on the data that has been published by the UGDP in several articles and the review of the UGDP study by the Biometric Society.

The UGDP study itself was funded as a grant by the National Institute of Arthritis, Metabolism and Digestive Diseases. It was begun in 1961 and, as you know, included 12 university medical school clinics. The coordinating center for the study and the data was and is the University of Maryland in Baltimore. The coordinating center director is Dr. Christian R. Klimt.

When the NIH awards a grant the only data requirements imposed by that grant are, generally, the submission of interim and final reports. Final reports are most often in

the form of journal publications, as has been the case with both the UGDP study itself and the Biometric Society report. It has not been the practice of the NIH to require that grantees submit their raw data, and no raw data was ever submitted in connection with the UGDP study. No provision of either the UGDP grant or the Biometric Society contract requires the submission to the NIH of raw data.

It appears, therefore, that the raw data is the property of the individual investigators and the coordinating center. Given that this is the case, this Department has, as stated previously, no authority to order that the data be made available in any form other than those reports required by the grant and the contract, and those reports have all been published.

I am informed that the raw data is now in the form of microfilm and is stored in a Maryland bank vault. I am also informed that Dr. Klimt, who states that he has spoken with the Attorney General of the State of Maryland on this subject, feels the data is protected from disclosure under Article 76A of the Annotated Code of Maryland. While I cannot, therefore, suggest it as a fruitful approach, it would appear that further efforts on your part should be directed to Dr. Klimt. His title and address are:

Professor and Director
Division of Clinical Investigation
University of Maryland School of Medicine
Baltimore, Maryland 21201

I regret that I cannot be of more help in this matter.

Sincerely yours,

/s/ THEODORE COOPER, M.D.
Theodore Cooper, M.D.
Assistant Secretary for Health

EXHIBIT R

CHAYET AND SONNENREICH, P.C.
ATTORNEYS AT LAW

6 FAYETTE STREET
BOSTON, MASSACHUSETTS 02110

(617) 227-0101

August 7, 1975

Theodore Cooper, M.D.
Assistant Secretary for Health
Department of Health, Education, and Welfare
Public Health Service
Washington, D.C. 20201

Dear Dr. Cooper:

I am in receipt of your letter of August 7, 1975 which denies the request of the Committee on the Care of the Diabetic (CCD) for the University Group Diabetes Program (UGDP) study raw data. I must confess that I am shocked by the fact that both the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have not studied the basic data of the UGDP study and have, instead, relied solely on journal articles in reaching the sweeping conclusions made with respect to oral hypoglycemics.

Given the nature of this five-year scientific dispute, it is astonishing that scientific personnel within the FDA and NIH would not have reviewed their basic data in light of the controversy which has raged within the scientific community concerning the validity of the UGDP study. It is our judgment that this failure of the FDA to so study this data amounts to gross scientific negligence and a real disservice to the public. It further casts even more doubt on

the conclusions reached by FDA in its regulations concerning the labeling of oral hypoglycemic drugs.

On behalf of the Committee on the Care of the Diabetic, I wish to inform you that your refusal to make available the raw data of the UGDP study on the theory that it belongs solely to Dr. Klimt is not acceptable either in law or in fact. Therefore, the CCD believes it has exhausted all administrative remedies possible and wishes to inform you that it will take the matter to court in the immediate future.

Yours truly,

/s/ NEIL L. CHAYET
Neil L. Chayet
Counsel
Committee on the Care of the Diabetic

cc: Dr. Alexander Schmidt

EXHIBIT S

(The following statement was telegraphed to the Commissioner of the Food and Drug Administration on December 1, 1970)

Statement On The Treatment of Diabetes

Uncritical and premature recommendations of the Food and Drug Administration regarding the treatment of diabetes mellitus are to be deplored. This is the conclusion reached by forty diabetes specialists who met on November 30, 1970, at the Sheraton-Boston Hotel to discuss their mounting concern for more than one million diabetic patients who have become increasingly disturbed because of newspaper stories alleging adverse effects from long term use of oral anti-diabetes agents.

The current controversy arose following a scientific presentation on June 14, 1970, at the annual meeting of the American Diabetes Association in St. Louis. At that time a group of 12 university centers known as the University Group Diabetes Program (UGDP) presented the results of an 8-year study of more than 800 diabetic patients subjected to different forms of treatment. This prospective cooperative clinical study *appeared* to show that administration of a sulfonylurea drug (tolbutamide) to mild adult-onset diabetes led to a greater death rate from cardiovascular disease than was found in three other groups treated with diet alone, a fixed dosage of insulin or a variable dosage of insulin. The report received widespread news coverage. Subsequently a letter sent by the ADA to its membership on October 27, 1970, supported the validity of this study, as did a report from the American Medical Association's Council on Drugs.

In late October, an official Food and Drug Administration "Current Drug Information" bulletin was sent to all physicians in the United States. Although based upon still unpublished findings, the letter contained far-reaching implications regarding the future treatment of diabetics. Portions of the FDA statement that may significantly affect diabetic management and greatly compromise the freedom of the physician to prescribe for his patients are as follows:

(1) "Oral hypoglycemic agents should be used only in diabetics with adult-onset, stable disease which cannot be controlled by diet alone and for whom insulin is unacceptable or impractical. A recently published study shows NO evidence that, in diabetics with adult-onset, stable diseases, therapy with a fixed dose of one such agent (tolbutamide) and diet is more effective in prolonging life than diet alone. The study also suggests that such a regimen may be less effective insofar as cardiovascular mortality is concerned than diet alone or than diet and insulin combined."

(2) In the words of Dr. Charles C. Edwards, Commissioner of Food and Drugs, "The initial and essential foundation for the management of adult-onset diabetes mellitus is diet and weight control. When the symptoms of the disease are adequately controlled by these measures, no other therapy is indicated. All oral hypoglycemic agents should be employed with caution and, if prescribed, then only when serious application of diet, or diet plus insulin has been proven ineffective in the judgment of the physician.

"A physician using hypoglycemic agents should familiarize himself with the cautionary material in the package inserts for these drugs and should adjust the dosage according to the individual patient's needs."

(3) Recommendations that extend the interpretation of the results of the UGDP study to the use of all currently avaliable oral hypoglycemic agnts are as follows: "The Food and Drug Administration recommends that the use of Orinase (tolbutamide) and other sulfonylurea type agents, Dymelor (acetohexamide), Diabinese (chlorpropamide),

Tolinase (tolazomide), should be limited to those patients with symptomatic adult-onset nonketotic diabetes mellitus which cannot be adequately controlled by diet or weight loss alone and in whom the addition of insulin is impractical or unacceptable. The oral hypoglycemic agents are not recommended in the treatment of chemical or latent diabetes, or in pre-diabetes, and are contraindicated in patients with keto-acidosis."

The actions of the FDA are based exclusively upon this solitary report by the UGDP. Yet, the absense of any similar observations during vast experience with large numbers of diabetic patients, both here and abroad, for periods up to 15 years in the use of tolbutamide and other oral hypoglycemic agents prompted this re-examination of the UGDP report.

The assembled group of diabetes specialists recognized numerous limitations of the UGDP study, including the following:

(1) There was no significant difference in overall mortality among the four treatment groups. Regarding the alleged excess of cardiovascular deaths in patients treated with tolbutamide, the lack of homogeneity of baseline risk factors in the 12 treatment centers invalidates statistical evaluation of the findings.

(2) Disagreement persists concerning the evaluation of the data by UGDP statisticians, since the application of different statistical methods has yielded contradictory results. For example, one independent analysis found no significant difference between tolbutamide and placebo groups with respect to cardiovascular deaths, either when tested separately within each of the 12 treatment centers or when the summed results of all 12 centers were analyzed.

(3) Spontaneous levelling of the claimed excessive mortality in tolbutamide-treated patients during the eighth and

last year of the UGDP study suggests that the alleged increase in cardiovascular deaths is not due to the administration of the drug.

Other matters were criticized severely by the group. The application of an arbitrary, constant dosage of tolbutamide differs radically from the customary clinical usage of the drug. The fact that therapy seemed to have little or no effect on maintaining normal blood sugar levels was attributed to the use of the fixed dosage of tolbutamide, which is also the shortest-acting of the sulfonylurea compounds. Furthermore, the well-known phenomenon of secondary failure known to occur in 30 percent or more of patients so treated was apparently ignored in this report as a possible cause for the elevated blood sugar levels observed.

Findings such as these made the group feel that the established treatment of diabetes was under significant pressure on the basis of experimental results of dubious validity.

The consensus of the meeting was that, before any further action is taken by regulatory agencies, the raw data should be made available to the scientific community at large.

The disastrous consequences of this report stem from the fact that it will tend to restrict treatment of patients with latent or asymptomatic hyperglycemic who do not respond to diet alone.

We categorically oppose the uncritical and premature recommendations of the FDA based on the single and still unpublished report of the UGDP, which is scientifically unacceptable to many specialists in diabetes. This unprecedented interference with the treatment of patients in a controversial area is not only outside the province of a governmental regulatory agency, but it has also damaged the welfare of more than a million diabetic patients.

The erroneous and insensitive manner in which purported information has been disseminated for the past six months has further burdened both physicians and the diabetic population at large with unwarranted anxiety over the treatment of the disease. The FDA action has been taken despite many contrary studies both there and abroad.

The recommendation restricts and all but prohibits the use of any and all oral agents in the treatment of diabetes, despite overwhelmingly favorable clinical experiences to the contrary. Furthermore, the therapeutic implications outlined are ambiguous and impossible to fulfill in accordance with established medical practice. The recent FDA recommendations for the treatment of diabetes seriously undermine the progress made on behalf of the diabetic through years of hard work and education, in the following respects:

(1) Diabetics and their families are confused, anxious, and uncertain of their physician's ability to guide their treatment. Progress in employment and insurance status will, in many instances, be pushed back a number of years by the enforced use of insulin treatment.

(2) The physician has had no basis for making his own decisions concerning the validity of the UGDP study. Yet, he is now forced, at least indirectly, into the use of principles in diabetic treatment prescribed by the FDA. Potentially, he is exposed to an unprecedented series of malpractice suits based on any occurrence of cardiovascular problems. Though these occur with great frequency in all diabetic patients, they may now be blamed upon the taking of an oral hypoglycemic agent.

The recommendations of the FDA tend to constitute the practice of medicine by specifying the order in which therapeutic programs are to be employed in the treatment of patients. This directive, if taken literally, will also prevent or seriously hamper future clinical research in this field. Furthermore, the FDA denies the value of chemical control of the disease, which emasculates any programs of diabetes detection as well as all public health measures in this area.

We request:

(1) Suitable modifications of the FDA Drug Information Letter. (2) Immediate reconsideration of currently proposed revisions of the package inserts demanded of the manufacturers of orai hypoglycemic agents, and (3) Further independent statistical and clinical analysis of the UGDP study based on raw data so far not available to the scientific community.

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EXHIBIT T

1.1 Specific Objectives

The aim of the study is principally to determine the relative effectiveness of four different treatment schedules in preventing the principal late complications of diabetes mellitus among diabetics able to live an asymptomatic life without insulin. The late complications of primary concern in this study are retinopathy, cardiac and peripheral vascular disease, nephropathy and possibly neuropathy. The four treatment groups are as follows:

a. standard diet plus placebo tablets;

b. standard diet plus a standard dose of tolbutamide;

c. standard diet plus a standard insulin dose; and

d. standard diet plus insulin in varying amounts dosed to maintain normoglycemia.

As yet, no positive proof has been presented that the treatment of diabetes with insulin or tolbutamide has a beneficial effect on the prevention, delay or alleviation of what are believed to be late complications of the disease. In the case of mild diabetes, where normal life is possible without the daily administration of insulin or tolbutamide, the disadvantage of such administrations from the health, convenience and economic point of view has to be weighed against possible advantages in the field of chronic complications. Only a long term prospective study with the inclusion of a negative control (diet plus placebo only) and a positive control (diet plus insulin ad. lib.) will shed some light on this question.

Since the advent of insulin in 1922 and more recently the antibiotics, mortality from diabetes and from the acute complications of the disease have been demonstrably reduced. It appears, however, that because of this prevention

of death, diabetics are increasingly able to procreate. This in turn has increased the gene frequency for the disease. As a matter of fact, there is tentative evidence that diabetes prevalence may actually be on the increase beyond what would be expected because of the aging of the U. S. population.

1.2 General Plan

In each of the participating clinics recently diagnosed cases of mild diabetes will be subjected to a four week observation period while treated with diet alone. If they remain free of signs and symptoms of uncontrolled diabetes excluding purely chemical abnormalities, they will be randomly allocated to one of the previously described four treatment groups. A separate random allocation schedule will be maintained for each participating clinic by the Coordinating Center. Each schedule assures equal numbers in the four treatment groups at certain intervals. No clinic will be informed of the treatment allocation schedule employed until after the study is completed. The placebo and tolbutamide treatments will be double blind, that is, neither the patient or the clinic staff will know whether a tablet treated patient is receiving placebo or tolbutamide. In the case of the insulin treatment groups only the patient will be unaware of the manner in which his treatment dosage is prescribed. In one case it will be on the basis of the patient's body surface and in the other case it will be determined by the physician in such a manner as to maintain normoglycemia.

A baseline evaluation of the patient's health status will be carried out upon entry of the patient into the study. This baseline examination for complications, as it will be referred to in this protocol, will consist of four individual examinations. One deals with the eyes, another with the heart, a third with the kidneys, and a fourth deals with the peripheral vascular system. The eye examination entails

measurement of visual acuity, the distant Snellen, and two retinal photographs of each eye. The heart examination consists of resting and post-exercise ECG's, systolic and diastolic blood pressure measurements and 6′ P-A teleochest x-ray. The kidney examination involves a urine protein determination and both blood and urine quantitative creatinine determinations. The peripheral vascular examination involves the use of soft tissue x-rays of both legs and feet as well as oscillometric measurements at three sites on both legs.

The patient will be required to keep a record of the tests for urine glucose and ketones that he will be asked to perform during the periods between clinic visits. At intervals of three months the patient will be asked to present himself at the clinic for what will be referred to as a quarterly examination. At this time the degree of control of the patient's diabetes will be determined. This determination will be based primarily upon the patient's test records and tests performed by the clinic for urine and blood glucose as well as on the clinical judgment of the physician. A temporary or permanent treatment change, and consequently failure of the originally prescribed treatment may result if ketonuria and/or signs and symptoms of uncontrolled diabetes are found.

One of the four examinations for complications will be coupled with each quarterly follow-up examination. In this manner a complete cycle of examinations will be completed in the course of any twelve month period. The order of coupling will be eye, heart, kidney and peripheral vascular. That is, the eye examination will be coupled with the first quarterly examination. The heart examination will be coupled with the second quarterly examination and so forth. These findings, in connection with the corresponding baseline examination results, can then be used to determine the onset and progression or regression of any complication.

Wherever possible the determination of critical endpoints for patients from all clinics will be entrusted to two or more specialists, who will arrive at their conclusions solely on the basis of the record of a specific examination, such as the ECG tracings, the fundus photographs or the soft tissue x-rays. Thus bias should be largely excluded and the consistency as well as the quality of the findings enhanced. The records will be forwarded from the clinics to the specialist consultants via the Coordinating Center and will only be identifiable by a code number. The consultants will be unaware of the treatment the patient is receiving. Through unannounced resubmission of already interpreted examination records to the same and to other expert consultants uniformity of interpretation will be checked at periodic intervals during the study.

The results from each clinic will be pooled provided certain conditions are met (see chapter 7) and subjected to statistical analysis at the Coordinating Center. The four treatment groups will be compared with respect to the number of deaths observed in each of the groups. In addition, the proportion among each treatment group developing one or more late complications will be compared. The proportion of clinic treatment failures among placebo, tolbutamide and standard dosage treatment groups will also be of interest. Some comparisons of interest cannot be made until the study has been completed because of their very nature, while others will be made at periodic intervals throughout the study. The analysis of the data will be facilitated with the use of IBM punch cards and IBM machines.

A detailed system to be employed in locating patients who are temporarily lost to the study, as well as a system to maintain a patient's cooperation when once in the study has been worked out (see chapter 5). These procedures must be employed to minimize the dropout rate. However, in those cases where a dropout does occur an annual evalu-

ation of the patient's status as to whether living or dead will be made. In these cases, as well as for non-dropouts, mortality constitutes a final endpoint for assessment of the relative merits of the different treatment groups.

Records for the entire cooperative study and periodic analysis of results will be centralized in the Coordinating Center. The Coordinating Center will also be responsible for maintaining uniformity in the records as well as in the laboratory techniques employed by each of the clinics. The Coordinating Center will also conduct ancillary studies aimed at either standardizing technical procedures or at developing them to such a degree that they will become a suitable diagnostic tool within the study.

1.3 Organization and Support

The study constitutes a collaborative effort of seven clinics and the Coordinating Center. The group chairman is Dr. Max Millner and the rapporteur is Dr. Harvey Knowles. Dr. Christian Klimt is director of the Coordinating Center and Dr. James Pratt is the liaison officer with the National Institute of Arthritis and Metabolic Diseases (NIAMD).

The study is being supported by individual research grants from the NIAMD to each of the participating clinics as well as to the Coordinating Center.

Support has been granted for the maximal permissible period of seven years. It is possible, however, that this period may have to be extended beyond this point in order to obtain conclusive results particularly with respect to some of the endpoints of interest.

The entire group will meet semi-annually to discuss current problems, proposed protocol changes, progress made, and available results. The site of the meeting will rotate among the locations of participating clinics. The post of co-chairman will be held by the host of the semi-annual meeting.

Members of the Coordinating Center will make periodic visits to each of the participating clinics. The purpose of these will be to aid in solution of problems peculiar to a particular clinic, as well as to review the record keeping system employed by the clinic. Occasionally the Coordinating Center may recommend an exchange of technical personnel if this is deemed necessary for purposes of training and standardization of technique.

1.4 History and Time Schedule of the Project

The development of this project can be divided into four phases. The first phase began in June, 1959, with a meeting in Atlantic City. At this time the basic objectives of the project were discussed and the principal aspects of the designs were set down. Additional meetings held in Cleveland during September, 1959, and January, 1960; in Los Angeles during January, 1960; in Brooklyn during May, 1960; in Miami during June, 1960; and in Boston during July, 1960, served to crystallize and expand upon the concepts set forth at the Atlantic City meeting.

STATISTICAL ANALYSIS OF THE DATA

7.1 Introduction

This chapter is an attempt to forsee the possible outcome of the current study as it relates to the data and conditions the analysis of the same. As such an attempt, it must be recognized that any statements concerning the analysis must, by the nature of being a forecast, be somewhat tentative. In the main we expect to be able to carry out the plans outlined herein; but it will be somewhat surprising if at least minor modifications are not necessary in many aspects. Thus, the proposed analyses set forth in this chapter are to be interpreted as provisional and subject to change as we learn by proceeding with the study.

All of the analyses to be performed must be made to coincide with the measurements to be collected. In this study, the "measurements" are the end points which have been agreed upon, and the time of occurrence of one of several end points in each patient, if they occur. Thus, the first step in considering the analyses to be performed is to have a clear statement of the conditions that will be classified as end points in any patient. (These will be provided at a later date).

7.2 The Analysis

a. Fixed Sample Size Approach Versus Sequential Analysis

In considering the statistical design of a study such as this one, the main question to be answered concerns the size of the group needed to be assigned to the various treatment groups. If this problem is to be settled a priori, certain other questions must be settled as is the situation in any case. However, the question

to be discussed here is one of approach; is it advisable to use pre-selected, fixed sample sizes (i.e., the "classical" method) or would it suit purposes better to use sequential methods. This latter method, due principally to the late Abraham Wald, has merits which recommend it. Primarily, the advantage of sequential analysis lies in the fact that, on the average, results of given precision can be obtained with fewer observations, i.e., with fewer patients. This might prove to be a worthwhile consideration when we face a long term follow-up study with its attendant risk of dropouts. It would seem advisable for the main aspects of the study to use, wherever possible, the technique of sequential analysis. Where such methods are not apropos, other techniques will be employed.

b. Simple Comparisons of Interest

For any particular end point, or for one end point after another has failed to materialize (in a specified sequence) the results of the various treatments will be compared. Thus, each of the other three treatments will be compared, for example for percentages of patients dying (within 1, 2, 3, etc., years) with the percentage dying among the negative controls, i.e., the diet plus placebo group. If there are no differences with this end point, then similar comparisons will be made with the next end point, e.g., with Grade II retinopathy. If, in addition, no differences can be discerned with this end point, then the next end point will be used as the basis of the comparisons—but in each case the comparisons are to be made for the overall groups of patients treated similarly.

It is to be noted here that no effort is to be made to segregate out individuals within treatment groups according to other relevant characteristics. This does not mean, however, that we shall not do such segregation;

it means only that at the first stage gross effects of treatment *over all* sub-groups is to be examined. This will be followed at a later stage by similar comparisons of more homogeneous sub-groups within treatment groups, e.g., groups of the same sex and age, possibly race and perhaps of similar socio-economic groups. However, the comparisons outlined previously will attempt to discern an overall treatment that is superior for all population sub-groups in inhibiting the late sequelae of diabetes mellitus.

c. Life Table Approach to Each of the End Points

It may prove more informative to examine the occurrence of each of the end points (in the specified sequence) on a life-table basis within treatment groups. Thus, the average expectation of life may be remarkably longer for one treatment than another. If this is not the case, it may be true that the average expectation of *survival without* a *given end point appearing* may be remarkably longer for one treatment than for another. If such information can be extracted from the data to be collected, it would be a valuable addition to the knowledge of the life history of the disease.

Again, such an analysis will be complicated by the fact that the probability of a particular end point may vary with

1). Time since onset of the disease

2). Patient's age

3). Patient's sex

4). A host of other factors,

It is then clear that an analysis of the kind outlined may be required for breakdown into more homogeneous sub-groups as indicated previously under part b above.

d. Competing Risks of End Points

It is also a distinct possibility that the occurrence of one end point may influence the appearance of another. For example, the appearance of renal pathology may so condition a patient as more frequently to precipitate peripheral vascular disease, or vice versa. Thus, it may be illuminating to investigate the appearance of the various end points, both in the presence of, and in the absence of, other end points or combinations of end points. This may give us some information on the influence of the competing risks in the development of the various end points.

7.3 Assumptions Underlying The Analysis

a. Pooling of Data From Several Different Sources

The nature of a cooperative study, such as one like this, is such that the data developed for the ultimate analysis is the composite of the data of the participating clinics. Such pooling of data from different sources has its hazards, the chief one involving the question of the comparability of the data from the different clinics. If the data were collected under the same circumstances, then it is a valid procedure to pool the data for a single analysis. Thus, in order that any one or several of the analyses previously contemplated be properly applied to the pooled data of this study, the following assumptions (at the very least) must be fulfilled:

1) The Overall Dropout Rate Must be Low

This is a simple assumption that is made to ensure that a sufficient number of patients remain in the study in order to observe a differential rate of development of complications among the several treatments. This assumption would be necessary whether or not the study were a cooperative one.

2) Treatment Failure Rates Among Treatments Do Not Differ Within a Clinic

This assumption is somewhat more subtle in its implications than the previous one. The importance of this assumption is that the whole purpose of the study is to test the differential effects of the various treatments on the *late* complications, while a treatment failure refers to a failure in the clinical management of the acute aspects of the disease. Thus, while the treatment-failures might provide valuable information concerning the efficacy of the various treatments in the management of diabetes, such treatment failures make it difficult to interpret data relating to late complications.

For example, suppose that the placebo treated (negative control) patients have a high proportion of treatment-failures as compared to the insulin standard patients. That is, after varying periods of treatment on the placebo, suppose that many placebo treated patients must be changed to insulin ad lib. In such a circumstance, how is a difference in incidence of late complications between, for example, the negative and positive control groups, to be interpreted? If diet plus insulin ad lib is truly effective over diet plus placebo in diminishing the incidence of late complications, such treatment failures will diminish *the difference in incidence* between the two groups. On the other hand, if diet alone is truly effective over diet plus insulin ad lib in diminishing the incidence of late complications, the treatment failures again diminish the *difference in incidence* between the two groups. And if there is *no difference to begin with* between the two regimens in diminishing the incidence of late complications, the results are equally (or more) equivocal; and it might be possible in this situation for the proponents of the insulin ad lib treatment to maintain (erroneously) that the fact that the large proportion of placebo treated patients were changed to insulin ad lib was the determinant in the equivalence of the incidence of the late complications. That is, we might find the insulin ad lib adherents erroneously claiming the credit for equality of incidence. These examples are cited merely to illustrate the potential difficulties ensuing from differential treatment failure rates among the various treatment groups.

3) Dropout Rates Among Treatment Group Within a Clinic Do Not Differ

This requirement, while not so subtle as the preceding one, is equally important. Dropouts are a form of self-selection, and differential dropout rates among the various treatment groups introduce the possibility of bias familiar to any study involving self-selection process. The whole process of random allocation to treatments, and the other devices introduced into any study such as this one are primarily concerned with the elimination of the possibility of bias. Every effort must be made to prevent dropouts which could, at once, vitiate all the other efforts to eliminate bias.

4) Uniform Treatment Failures and Dropouts Among Treatments and/or Among Clinics

As long as treatment failures and dropouts are uniform within a clinic (assumptions 2 and 3), comparisons among treatments are valid within the clinic. However, when the data are to be pooled for combined analysis, another facet must be verified in addition. Such a facet is the treatment failure rate and dropout rate *among* clinics. If both of these rates are (each by itself) uniform across clinics

then the pooling of the data from the several clinics may be safely accomplished. But if either of these rates shows a marked variation from clinic to clinic, then *again* there may be trouble in attempting to pool the data from the several clinics.

b. Difficulties Encountered if Assumptions Not Satisfied

It is possible to anticipate the kinds of difficulties that will be encountered if the assumptions 1 through 4 listed above are not satisfied. It is advisable to list these difficulties primarily to alert the participants in the study in order that they make every effort to avoid these hazards. In addition, listing the sequelae will serve to lay down certain "ground rules" in advance, in case it becomes necessary to make use of them.

1) If assumption 1 is not fulfilled, the whole point of the study will be missed. That is, there will be too few patients remaining in the study for a sufficiently lengthy period of time for the end points to be reached. "Too few" in this context means "too few in order to allow a satisfactory resolution of the relative effectiveness of the competing treatments". More simply stated, this means that a high dropout rate may leave residual sample sizes in the various treatment groups so small as to diminish the power of the statistical tests to be used to such a point that unequivocal findings will not be possible.

2) If either assumption 2 or assumption 3 (or both) is (are) not fulfilled in any clinic(s) then the trouble is real. First of all, the data among clinics becomes non-comparable; and the clinics in which the assumption(s) is (are) not satisfied may no longer be pooled with the total group. Even more of a problem is the value of the data from such a clinic for any analysis.

While it may be argued that the data from such a clinic may be analyzed separately to advantage, this argument appears open to question. Differential dropout rates certainly, and differential treatment-failure rates possibly, are selection proceses on the patients. That any selection process, and these in particular, may introduce a bias in the results is a constant spector to be avoided; where such selection cannot be avoided, the results obtained are of much diminished value for establishing results. It is true that we have some plans for analysis taking into account treatment-failures; whether these will be as sound when such failure rates differ among treatments will require further investigation. But in no manner have we been able to grapple with the question of differential dropout rates; the potential biases introduced by this self-selection process do not appear to lend themselves to any method of statistical adjustment.

3) If assumption 4 is not fulfilled, then again we have real trouble. Differential dropout rates among clinics leave us in much the same equivocal position vis-a-vis self-selection biases as does this same problem within clinics. Nothing more need be said concerning this question.

However, the question of differential treatment failures among clinics introduces a whole new set of problems. As long as we remain within a clinic, differential treatment failure rates have been the result of the same group of clinicians and are, presumably, based on the same set of diagnostic criteria, the same level of diagnostic skill, and (most important) the same set of (unconscious) biases in the investigators. But when we consider the same problem across clinics, we may be dealing with *different* sets of diagnostic criteria, *different* levels of diagnostic

skill, and (most important) *different* (unconscious) biases in the investigators.

The last mentioned item is of paramount importance. It is in the (unconscious) prejudices of the investigators for or against some treatment that may lead to the introduction of biases in the results. For example, an investigator favorable to insulin may (unconsciously) lend little weight to a patient's complaint of nocturia if the patient is being treated with insulin-standard; and this same complaint may loom large if the patient is being treated with pills —either tolbutamide or placebo. Or it is equally possible for the investigator to lean over backwards and react in exactly the opposite fashion. The important point is that, so long as it is impossible to conduct the study on a double blind basis, the investigator's (unconscious) set of biases concerning the relative merits of the treatments *may introduce biases in his deciding what are treatment failures.* Differential treatment failure rates among clinics may undoubtedly be defended on the basis of dealing with different populations: "my population is older"; "my set of patients is predominantly of a different genetic origin"; "my clinic group is of a lower socio-economic class and has less understanding of the problem"; etc. Such may all be true, but it is rather difficult to document such arguments objectively. And it is always possible that, even granting these defenses as correct, it is still true that biases have crept in which damage the data beyond repair.

EXHIBIT U

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Food and Drug Administration

Rockville, Maryland 20852

September 19, 1975

Received Sept. 24, 1975, Chayet and Sonnenreich, P.C.

In reply refer to: File No. F 75-6515

Ms. Marien E. Evans
Chayet and Sonnenreich, P.C.
Attorneys at Law
6 Fayette Street
Boston, Massachusetts 02116

Dear Ms. Evans:

This is in response to your letter of August 22, 1975, denominated as a request pursuant to the Freedom of Information Act, but actually a request for information not a document.

A Notice of Claimed Investigational Exemption for a New Drug (IND) was not filed by the University Group Diabetes Program, any of the investigators involved in the program, or the manufacturers of the drugs tolbutamide or phenformin hydrochloride in 1961. The statutory requirement that an IND be filed pursuant to regulations promulgated by the Department was not added to the Federal Food, Drug, and Cosmetic Act until passage of the Drug Amendments of 1962, P.L. 87-481, effective January 8, 1963 (28 F.R. 183).

For your information, two separate IND's were subsequently filed by the UGDP Program. One of those was filed in 1967 and the other in 1971 for administrative record-keeping purposes only.

Sincerely,

/s/ SAM D. FINE
Sam D. Fine
Associate Commissioner
for Compliance

EXHIBIT V

CHAYET AND SONNENREICH, P.C.
Attorneys at Law

6 Fayette Street
Boston, Massachusetts 02116

(617) 357-0202

September 26, 1975

Mr. Richard A. Merrill
Chief Counsel
Food and Drug Administration
5600 Fishers Lane
Room 6-57
Rockville, Maryland 20852

Dear Mr. Merrill:

I am attaching, for your information, a copy of the letter we received from Associate Commissioner Sam D. Fine in response to a request made on behalf of the Committee for the Care of the Diabetic to determine whether or not an IND was filed by the University Group Diabetes Program at the initiation of its project. As you can see from Associate Commissioner Fine's letter of September 18, 1975, an IND was not filed until 1967 and again in 1971, and these were filed, according to Associate Commissioner Fine, "for administrative recordkeeping purposes only."

On behalf of the Committee for the Care of the Diabetic, I would like to know why such a project was permitted to proceed from 1961 through 1967 without the filing of an IND, and the nature of subsequent INDs filed in 1967 and 1971. Our reading of the Federal Food, Drug and Cosmetic Act would indicate that such a study would require, as a matter of law, the filing of an IND. Further, our review of

the law and regulations thereunder did not yield any special regulations relating to the filing of INDs "for administrative recordkeeping purposes only."

Before proceeding any further in this matter, we are formally requesting your legal opinion, as principal legal officer of the Food and Drug Administration, as to the legality of this UGDP study. Since it is our contention and belief that the study was carried out in clear violation of federal law, we would be most interested in knowing what actions, if any, are anticipated by the Food and Drug Administration in this regard.

I look forward to an early reply to this inquiry.

Yours truly,

/s/ Neil L. Chayet
Neil L. Chayet
Counsel
Committee for the Care of the Diabetic

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

Peter H. Forsham, *et al., Plaintiffs*

v.

David Mathews, *et al., Defendants*

MOTION FOR EXPEDITED RELIEF

Now come plaintiffs in the above entitled action and move pursuant to the provisions of 5 U.S.C. § 552 and Rule 65(a) of the Federal Rules of Civil Procedure for an Order granting plaintiffs expedited relief compelling the immediate production of the raw data of the University Group Diabetes Program and the draft report of the Biometric Committee, all as more fully set forth in the Complaint, Memorandum of Points and Authorities in support of plaintiffs' Complaint, and Order on file with this Court.

Plaintiffs further move that hearing on this Motion be consolidated with trial of the action on the merits.

Respectfully submitted

Chayet and Sonnenreich, P.C.

By /s/ Neil L. Chayet
Neil L. Chayet

/s/ Harvey W. Freishtat
Harvey W. Freishtat

Attorneys for Plaintiffs

6 Fayette Street
Boston, Massachusetts
617/357-0202

IN THE
UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, *et al., Plaintiffs*

v.

DAVID MATHEWS, *et al., Defendants*

MOTION OF DEFENDANT, DR. CHRISTIAN R. KLIMT, TO DISMISS AND TO QUASH SERVICE OF PROCESS

Defendant, Dr. Christian R. Klimt, by Francis B. Burch, Attorney General of Maryland, David H. Feldman and Mary Elizabeth Kurz, Assistant Attorneys General, pursuant to Rule 12(b) of the Federal Rules of Civil Procedure, moves for an order dismissing the action filed herein and quashing the service of process as to the aforementioned Defendant. The grounds for the Motion are as follows:

1. Lack of jurisdiction over the person; and
2. Insufficiency of process; and
3. Insufficiency of service of process.

In support of the Motion, the Court is respectfully referred to the Memorandum accompanying this Motion.

Respectfully submitted,

/s/ FRANCIS B. BURCH
Francis B. Burch
Attorney General of Maryland

/s/ DAVID H. FELDMAN
David H. Feldman
Assistant Attorney General

/s/ MARY ELIZABETH KURZ
Mary Elizabeth Kurz
Assistant Attorney General
201 W. Preston St. (Lobby Level)
Baltimore, Maryland 21201
(301) 383-6016
Attorneys for Defendant,
Dr. Christian R. Klimt

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, HENRY DOLGER, HOLBROOK S. SELTZER, as they are members of the Committee on the Care of the Diabetic, *Plaintiffs*,

v.

DAVID MATHEWS, Secretary of the Department of Health, Education, and Welfare; THEODORE COOPER, Assistant Secretary of Health, Department of Health, Education and Welfare; ALEXANDER M. SCHMIDT, Commissioner of the Food and Drug Administration; G. DONALD WHEDON, Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases; CHRISTIAN R. KLIMT, *Defendants*.

OPPOSITION TO MOTION TO DISMISS AND TO QUASH SERVICE OF PROCESS

Original Filed Nov. 24, 1975

Now come plaintiffs in the above-entitled action and oppose defendant Klimt's Motion to Dismiss and to Quash Service of Process for reasons set forth in the accompanying Memorandum.

Respectfully submitted,

NEIL L. CHAYET

HARVEY W. FREISHTAT

CHAYET AND SONNENREICH, P.C.
Six Fayette Street
Boston, Massachusetts 02116

Telephone no.: (617) 357-0202

EXHIBIT B

UNIVERSITY OF MARYLAND

School of Medicine

Institute of International Medicine

Baltimore, Maryland 21201

Division of Epidemiology and Biostatistics

TO: NIAMD Study Section on Epidemiology and Disease

FROM: Christian R. Klimt, M.D., Dr. P. H. and Ovid B. Bush, Jr., M.D.

SUBJECT: Pending grant application entitled "Prevalence of Diabetes and Vascular Complications in Japan"

This is in answer to the request made by the site visiting committee for an elaboration of certain points pertinent to the above grant application. These points can be grouped as follows:

1) The history of the development and conduct of the preceding study entitled "Geographic Pathology of Diabetes in Japan" under the principal investigatorship of Dr. Daniel B. Stone at the University of Iowa.

2) Amplification of reasons for locating the proposed study in Japan. Results with regard to feasibility of proposed study obtained from pilot studies. Summary of scientific results obtained and lessons learned from current Iowa based study.

RE (1):

The original grant application, submitted three years ago by Dr. Stone from the University of Iowa essentially contained the study plan as it is now being proposed. The plan can be divided into four phases:

Phase 1: Hospital based study of selected diabetics in Japan using clinical and laboratory procedures comparable to those developed for and by the University Group Diabetes Program in the USA.

Phase 2: Pilot field studies for diabetes prevalence intended to develop technically suitable as well as practical survey methods.

Phase 3: Diabetes prevalence field study in selected localities in Japan representing different types of socio-economic communities.

Phase 4: Follow-up study for vascular complications and diet patterns of persons aged 30 and over representing the above communities. Three groups are to be followed depending on plasma glucose levels obtained under standardized conditions.

The original grant application was partially approved for a period of three years, permitting the conduct of Phase 1 and Phase 2 studies. By July, 1966 the hospital based study has followed 130 patients and four pilot field studies have been completed. This grant will continue until the end of March 1967. The present grant is intended to provide for Phases 3 and 4, i.e., the diabetes prevalence study based on approximately 20,000 persons aged 30 and over representing seven selected communities, and Phase 4, the follow-up study of approximately 1,000 persons, 250 with one hour post glucose challenge plasma values under 160 mg percent, 250 in the gray zone with corresponding plasma glucose values between 160-209 mg percent, and about 500 persons with plasma glucose values of 210 mg percent or more, i.e., the diabetic group. These 1,000 persons will be followed annually for the appearance of vascular complications in the heart, the eye, the kidney and the peripheral vascular tree.

While important information is expected to emanate from Phases 1 through 3, the core of the study is an evaluation of the rate of the appearance and development of

vascular complications by class of plasma glucose level (i.e., the presumably non-diabetic, the gray zone, and the presumably diabetic class) and the cross correlation of vascular complication rates with environmental factors such as diet.

For organizational and technical reasons it has been agreed with Dr. Daniel B. Stone (see letter attached to grant application) to transfer the study from the University of Iowa to the University of Maryland and to change the principal investigatorship from Dr. Stone to Drs. Klimt and Bush. The emphasis in Phases 3 and 4 of the study on epidemiology and statistics and on field work in Japan makes this transfer a logical one.

RE (2):

This concerns the reasons for locating the study in Japan.

A) Among the developed countries, Japan has the lowest mortality rate for diabetes. It may also have a low diabetes prevalence. Japan has a low mortality from coronary artery disease coupled with high hypertension and stroke rates. Small scale studies and clinical impressions indicate that severe vascular complications are quite rare among diabetics in Japan. The prevalence of diabetes and the rate, as well as severity of vascular complications, must be ascertained in a population based study with criteria and techniques widely used and accepted in the U.S.

B) A wide variety of diets is found in Japan. The traditional rural areas show a high carbohydrate, low fat, low animal fat, and low cholesterol diet.

On the other hand, in urban and suburban areas a cultural transition to Western type diets with high fat intake is taking place. The caloric intake does not vary much and is comparable to caloric intake in the United States. Diet patterns can be uniquely found and correlated to diabetes prevalence and onset as well as progression rates of vascular complications in Japan.

C) The University of Iowa hospital based study gives support to the hypothesis of differences in the frequency and pattern of vascular complications in Japanese diabetics.

While on the one hand, small vessel disease, particularly in the eye, is found very frequently in a selected group of diabetics, these same diabetics show very infrequent large vessel disease in the peripheral arterial tree. These findings are in strong contrast to data obtained in the University Group Diabetes Program where newly diagnosed diabetics of the same age range show equal frequencies of small and large vessel disease, the latter being about four times as frequent as found in the Japanese patients. One might lean to the conclusion that small vessel disease is an integral part of diabetic pathology, while peripheral arteriosclerosis, though possibly enhanced by diabetes, is largely influenced by environmental factors, quite possibly the type of diet consumed.

D) The pilot prevalence surveys have been conducted as part of multipurpose surveys using various screening and diagnostic techniques. The data are small in scale and, therefore, difficult to interpret and are not suitable for pooling of results as by design different techniques have been used in each pilot study. Having in mind the above restrictions, we find prevalence figures which are *not* unusually low when compared to data from the U.S. The pilot field studies had as their prime purpose the study of methods and feasibility. We have learned not to use a step-wise program beginning with urine or random blood sample screening to be followed by a glucose tolerance test in positive "screenees".

In the last pilot survey, completed during July of 1966, a group of 500 individuals, preselected to represent a defined population, were invited to come on a given date to a clinic for a short glucose tolerance test. The test was to be given to the overnight testing individual during the morning. A 50% initial response rate was obtained without any

preceding information either to the persons tested or to the medical community. This may be considered a satisfactory initial response rate which, of course, will be improved upon in the future during the actual survey by home visits, medical and lay propaganda and flexible clinic hours. It should be noted that these survey methods are in accordance with the recommendations passed by a symposium sponsored by the U.S. PHS on population based studies on diabetes (Washington, October, 1964).

E) In addition to the above mentioned scientific reasons for wishing to locate this study in Japan, the following organizational reasons may be given:

i) Two M.D.'s from the University of Osaka (i.e., Dr. A. Sasaki, and Dr. T. Suzuki) will have been trained for two years in epidemiology and statistical methods, including computer programming at the University of Maryland in Baltimore by the first half of 1967. These two doctors will both be available full time for participation in this study.

ii) A complete field survey team has been assembled and trained in survey procedures.

iii) Laboratory methods have been set up at the University of Osaka on a Technicon autoanalyzer for determinations of glucose, BUN, creatinine and cholesterol. The results have been compared with the ones of duplicate samples obtained in the U.S. and found to be satisfactory.

iv) Mrs. Joan Bickel, research dietician of the University of Iowa has given training to Japanese dieticians on diet survey techniques.

v) Clinicians have been trained in the use of techniques, developed for and by the University Group Diabetes Program particularly with regard to: Fundus photographs, soft tissue X-rays, resting and post-

exercise ECG's, kidney function tests, and clinical examinations including skinfold measurements and biothesiometric measurements for vibratory sensitivity. They will continue to be available for this study.

vi) An administrative organization has been developed by Dr. Bush in Osaka which is capable of assuring liaison among the participating groups in Japan and with the University of Maryland in Baltimore and handling fiscal matters in accordance with University and National Institute of Health requirements.

vii) Certain equipment and facilities are already available (i.e., one autoanalyzer, a Zeiss camera for fundus photography, a spectrophotometer, a minus 20 degree Centigrade deep freeze, office equipment and an electric calculator.

viii) Strong relations have been forged among the participating universities, i.e., Maryland, Iowa and Osaka, through the current study, though the training program of Japanese M.D.'s in Baltimore and through prolonged visits of Dr. Seki and Dr. Wada to the United States.

ix) The cost of the proposed study could not be matched for a comparable effort in the U.S. This is mainly due to the lower Japanese salary scales.

x) The availability of technical expertise including expert readership for clinical records through the University Group Diabetes Program (UGDP). These facilities will also be available for the Japanese records and will assure comparability of findings between the two studies. Dr. C. R. Klimt and his staff in Baltimore function as the Coordinating Center for the UGDP thus assuring liaison with the proposed study in Japan. In addition, Dr. Max Miller of Cleveland, who is chairman of the UGDP, will be available as clinical diabetes consultant.

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE — PUBLIC HEALTH SERVICE — NATIONAL INSTITUTES OF HEALTH — DIVISION OF RESEARCH GRANTS

EXHIBIT C

EXPENDITURES REPORT — RESEARCH GRANTS

LEAVE BLANK: A.P. 31 R.P. [5]

READ INSTRUCTIONS ON PAGE 4 BEFORE COMPLETING THIS FORM

TYPE OF REPORT: ☐ PRELIMINARY ☒ FINAL

PERIOD COVERED BY THIS REPORT: September 1, 1960 — August 31, 1962

PHS GRANT NO: AP-[illegible] (C1)

1. AMOUNT OF GRANT FUNDS RECEIVED FROM PUBLIC HEALTH SERVICE	$ 27,160 00	
2. AUTHORIZED TRANSFERS	$	
3. FUNDS AVAILABLE FOR EXPENDITURE		$ 27,160 00
4. INTEREST EARNED (If any) TO BE RETURNED TO PHS, D. H. E. W.	$	
EXPENDITURES		
5. TOTAL DIRECT COSTS COVERED BY THIS REPORT (Item 2, Column 7)	$ 22,963 22	
6. INDIRECT COSTS (15 % of Line 5)	$ 3,114 48	
7. TOTAL EXPENDITURES PREVIOUSLY REPORTED FOR THIS GRANT PERIOD	$	
8. TOTAL EXPENDITURES TO DATE (Add lines 5, 6, and 7)		$ 26,107 70
9. CASH BALANCE (Line 3 minus line 8)		$ 1,052 30
10. DEDUCT OBLIGATIONS OUTSTANDING FOR PERMANENT EQUIPMENT (Include also on line 11)		
DATE OBLIGATED / ITEM	$	
NO LETTER NECESSARY	$	
	$	
11. TOTAL OBLIGATIONS OUTSTANDING		-0-
12. FREE OR UNOBLIGATED BALANCE (Line 9 minus line 11)		$ 1,052 30

INF. [illegible] REFER TO C1

I hereby certify that the foregoing report is true in all respects and that the expenditures and obligations have been made within the provisions of the grant and for the purposes set forth in the application recommended by the National Advisory Council.

INSTITUTION	MAILING ADDRESS *
University of Minnesota	Minneapolis 14, Minnesota
PLEASE TYPE NAME OF PERSON SIGNING REPORT	TITLE OF PERSON SIGNING REPORT
R. H. Elliott	Research Contract Coordinator

JAN 18 1962
(DATE)

(SIGNATURE)

I hereby certify that the above expenditures and obligations listed on this report were made with my approval.

(INVESTIGATOR)

*If the Financial Records on this Grant are not kept at this address, indicate below where Records will be available for audit.

JC:/c's

BEFORE PREPARING REPORT SEE INSTRUCTIONS ON PAGE 4

SUPPLEMENTAL SCHEDULES

A-1. EXPENDITURES FOR PERSONNEL: SALARIES AND WAGES (ITEMIZE)

NAME	POSITION	MONTHS EMPLOYED	AMOUNT PAID
1. Beverly Anderson	Key Punch Operator	P.T.	$ 747.62
2. Virginia Belcher	Senior Clerk	P.T.	619.56
3. Charlotte Sidne	Senior Clerk	P.T.	593.32
4. Curtis Heinert	Research Fellow	$11\frac{1}{2}$	7,141.24
5. Donna Springer	Secretary	$11\frac{1}{2}$	3,231.50
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
TOTAL			$ 12,399.55

B. EXPENDITURES FOR TRAVEL (ITEMIZE)

DATE OF TRAVEL	NAME OF TRAVELER AND DESTINATION	TRANSPORTATION CHARGES	OTHER TRAVEL ALLOWANCES	TOTAL
1. IX 8/1/60	Dr. Christian Flint, Rochester, Minn.	$ 12.00	$	$ 12.00
2. IX 10/29-11/4/60	Dr. Christian Flint, San Francisco, Calif.	266.85	154.53	421.38
3. IX 5/19-5/20/60	Dr. Christian Flint, Cleveland, Ohio	85.30	25.24	110.54
4. IX 12/4-12/17/60	Dr. Christian Flint, [illegible], [illegible], New York, Washington D.C., Baltimore & Boston	144.90	234.52	[illegible]
5. IX 12/4-12/17/60	Dr. Curtis Heinert, Cincinnati, Williamson, Charleston, New York, Washington D.C., Baltimore & Boston	144.90	231.85	376.75
XV. 3/12-3/13/61	Dr. Christian Flint, Cleveland	85.30	32.83	118.13
3/12-3/14/61	Dr. Curtis Heinert, Cleveland	[illegible]	43.16	128.46
3/13-3/1[illegible]/61	Dr. [illegible], Baltimore	[illegible]	53.53	173.[illegible]3
[illegible]/61	Dr. [illegible], [illegible]	[illegible]	81.[illegible]	1[illegible].41
[illegible]/61	Dr. Curtis Heinert, [illegible]	[illegible]	[illegible]	[illegible]
7/7-[illegible]/61	Dr. Christian Flint, [illegible]	[illegible]	[illegible]	[illegible]
TOTAL		1,620.00	1,332.70	2,922.70

PHS-421 Page 2

JUN 24 1963

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PHS-421
REV. 3-69

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH GRANTS

FORM APPROVED
BUDGET BUREAU NO. [illegible]

EXPENDITURES REPORT — RESEARCH GRANTS

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COM	N COM

READ INSTRUCTIONS ON PAGE 4 BEFORE COMPLETING THIS FORM

TYPE OF REPORT	FROM	TO	PHS GRANT NO.
☐ PRELIMINARY ☒ FINAL	[illegible], 1961	[illegible], 1962	[illegible]

AMP 68/76

1. AMOUNT OF GRANT FUNDS RECEIVED FROM PUBLIC HEALTH SERVICE	$ 30,271.00	
2. AUTHORIZED TRANSFERS from grant AP-1357(C1)	$ 3,052.30	
3. FUNDS AVAILABLE FOR EXPENDITURE		$ 33,323.30
4. INTEREST EARNED (if any) TO BE RETURNED TO PHS. D. H. E. W.	$	
EXPENDITURES		
5. TOTAL DIRECT COSTS COVERED BY THIS REPORT (includes A through E)	$ 25,420.54	
6. INDIRECT COSTS (____% of line 5) (taken to allotment)	$ 3,953.62	
7. TOTAL EXPENDITURES PREVIOUSLY REPORTED FOR THIS GRANT PERIOD	$ -0-	
8. TOTAL EXPENDITURES TO DATE (add lines 5, 6, and 7)		$ 33,374.16
9. CASH BALANCE (line 3 minus line 8)		$ 51.16
10. DEDUCT OBLIGATIONS OUTSTANDING FOR PERMANENT EQUIPMENT (as of date of this report)		

DATE OBLIGATED	ITEM	
		$
		$
		$

NO LETTER NECESSARY

11. TOTAL OBLIGATIONS OUTSTANDING		$ -0-
12. FREE OR UNOBLIGATED BALANCE (line 9 minus line 11)		$ 51.16

I hereby certify that the foregoing report is true in all respects and that the expenditures and obligations have been made within the provisions of the grant and for the purposes set forth in the application recommended by the National Advisory Council.

INSTITUTION	MAILING ADDRESS *
University of Minnesota	Minneapolis 14, Minnesota
PLEASE TYPE NAME OF PERSON SIGNING REPORT	TITLE OF PERSON SIGNING REPORT
R. H. Elliott	Research Contract Coordinator

MAY 22 1963

(DATE) (Signature)

I hereby certify that the above expenditures and obligations listed on this report were made with my approval.

*If the Financial Records on this Grant are not kept at this address, indicate below where Records will be available for audit.

(INVESTIGATOR)

BEFORE PREPARING REPORT SEE INSTRUCTIONS ON PAGE 4

A-1. EXPENDITURES FOR PERSONNEL SALARIES AND WAGES (ITEMIZE)

NAME	POSITION	MONTHS EMPLOYED	AMOUNT PAID
1. Curtis L. Hoiseth	Research Fellow	12	$ 7[illegible] 00
2. Doris H. Spelgum	Secretary	10	277 60
3. Virginia P. Fiddler	Statistical Clerk	16	329 71
4. Charlotte F. Niles	Junior Clerk	P.T.	173[illegible] 51
5. Beverly J. Anderson	Key Punch Operator	P.T.	131 17
6.			
7. Social Security Contributions			307 33
8. SUI Contributions			162 [illegible]
9. Workmen's Compensation Insurance			53 14
10.			
11.			
12.			
13.			
14.			
15.			
TOTAL			$ 1[illegible]

B. EXPENDITURES FOR TRAVEL (ITEMIZE)

DATE OF TRAVEL	NAME OF TRAVELER AND DESTINATION	TRANSPORTATION CHARGES	OTHER TRAVEL ALLOWANCES	TOTAL
1. 11/15-11/17/61	Curtis Hoiseth-Detroit, Mich.	$ 77 00	$ 112 35	$ [illegible] 35
11/26-12/1/61	Curtis Hoiseth-Dallas, Tex.		82 85	82 85
11/26-12/1/61	Curtis Hoiseth-Dallas, Tex.		190 10	190 10
1/31-2/7/62	Curtis Hoiseth-St. Clair Mich	110 65	18 30	129 [illegible]
2/10-2/17/62	Curtis Hoiseth-Cincinnati, Ohio			
4.	[illegible]	210 00	135 30	[illegible]
11/21/61	Curtis Hoiseth-Dallas, Tex.	117 [illegible]		117 [illegible]
12/21/61	Curtis Hoiseth-Dallas, Tex.	117 [illegible]		117 [illegible]
TOTAL	[illegible]	$ [illegible]		$ [illegible]

PHS-421 Page 3

U. S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
DIVISION OF [illegible] GRANTS

EXPENDITURES REPORT
RESEARCH GRANTS

READ INSTRUCTIONS ON PAGE 4 BEFORE COMPLETING THIS FORM

TYPE OF REPORT: ☐ PRELIMINARY ☒ FINAL

PERIOD COVERED: [illegible] to 12/31/61

PHS GRANT NO. MH-06076-03

1. AMOUNT OF GRANT FUNDS RECEIVED FROM PUBLIC HEALTH SERVICE	$ 93,342 00	
2. AUTHORIZED TRANSFERS	$ 1,322 23	
3. FUNDS AVAILABLE FOR EXPENDITURE		$ 99,664 23
4. INTEREST EARNED (if any) TO BE RETURNED TO PHS, D. H. E. W.	$	
EXPENDITURES		
5. TOTAL DIRECT COSTS COVERED BY THIS REPORT (Schedule A Item E)	$ 83,226 02	
6. INDIRECT COSTS (20 % of Direct Costs) 82,191.02	$ 16,438 21	
7. TOTAL EXPENDITURES PREVIOUSLY REPORTED FOR THIS GRANT PERIOD	$	
8. TOTAL EXPENDITURES TO DATE (Add Items 5, 6, and 7)		$ 99,664 23
9. CASH BALANCE (Item 3 minus Item 8)		$ -0-
10. DEDUCT OBLIGATIONS OUTSTANDING FOR PERMANENT EQUIPMENT (Included on this report)		
DATE OBLIGATED / ITEM	$	
	$	
	$	
11. TOTAL OBLIGATIONS OUTSTANDING		$
12. FREE OR UNOBLIGATED BALANCE (Item 9 minus Item 11)		$ -0-

4/4/62

I hereby certify that the foregoing report is true in all respects and that the expenditures and obligations have been made within the provisions of the grant and, for the purposes set forth in the application recommended by the National Advisory Council.

[illegible] University of Maryland	22 S. Greene St., Balto., Md. (21201)
[illegible]	Controller/Administrator

4/4/62
(DATE)

I hereby certify that the above expenditures and obligations listed on this report were made with my approval.

(PRINCIPAL INVESTIGATOR)

Christine Niles, M.D.
Dr. P.H.

*If the Financial Records on this Grant are not kept at this address, indicate below where Records will be available for audit.

BEFORE PREPARING REPORT SEE INSTRUCTIONS ON PAGE 4

B. Expenditures for Travel
FO1-AM-05576-03 FED KT-V541

Date	Name of Traveler and Destination	Transp. Charges	Other Travel Allow.	Total
9/30-10/2/64	[illegible],Christian R.-Washington,D.C.	$ 9.50	$ 19.83	$ [illegible]
9/30-10/1/64	Meinert,Curtis L.-Bethesda,Md.	12.70	20.83	33.53
10/3-10/6/64	Klint,Christian R.-New York	45.90	102.85	148.75
10/3-10/7/64	Meinert,Curtis L.-New York	12.70	101.02	113.72
9/1-9/4/64	Ho,Irvin P. - New York	41.70	105.00	146.70
10/23-25/64	Bowman,Jacob E.-Chicago,Ill.	64.70	45.14	109.84
10/27/64	Meinert,Curtis L.-Washington,D.C.	11.00	2.15	13.15
10/21-25/64	Suzuki,Tokichiro-Chicago,Ill.	79.50	32.17	111.67
10/23-25/64	Klint,Christian R.-Chicago,Ill.	93.00	50.14	143.14
10/23-25/64	Meinert, Curtis L.-Chicago,Ill.	85.45	46.74	132.19
9/3-11/64	Ho,Irvin P.-Chicago,Ill.	79.00	38.92	117.92
9/1-4/64	Thomas, David D.-New York	8.70	107.55	116.25
9/30-10/64	Meinert, Curtis L. - Minneapolis	9.50	46.75	56.65
8/28-31/64	Meinert,Curtis L. - New York	21.25	48.70	69.95
[illegible]	[illegible],Christian R.-Washington,D.C.	35.05	74.30	110.35
1/24/64	Klint, Christian R.-Bethesda,Md.	9.00	1.25	10.25
/12/65	Klint, Christian R.-Silver Springs,Md.	9.00	1.00	10.00
/6/65	Klint, Christian R.-Minneapolis,Minn.	11.00	-0-	11.00
2-5/65	Tack,O. Charles-Chicago,Ill.	85.50	32.75	118.25
22-27/65	Belcher,Virginia P.- Baltimore,Md.	86.60	72.43	159.03
/20/65	Kozen,Alfred - College Park, Md.	123.99	88.88	212.87
/23/65	Klint,Christian R.-Bethesda, Md.	6.00	-0-	6.00
/27/65	[illegible],Christian R.-Washington,D.C.	11.00	-0-	11.00
/21-25/65	Klint,Christian R.-San Juan,P.R.	9.50	9.20	[illegible]
/21-25/65	Meinert,Curtis L.-San Juan,P.R.	148.50	139.75	288.25
/21-25/65	Ho,Irvin P. - San Juan,P.R.	140.70	122.50	263.20
/21-23/65	Bowman,Jacob E. - San Juan,P.R.	146.80	139.70	286.50
12/65	[illegible],Christian R.-Washington,D.C.	253.70	50.30	304.00
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
28-10/65	Klint,Christian R.-New York	52.20	6.75	58.95
11-13/65	Meinert,Curtis L.-Minneapolis	55.65	36.54	92.19
	Local Travel	135.85	58.00	193.85
26/65	Wilson,P. - Washington, D.C.	1.75	-0-	1.75
23-24/65	Miettinen,Olli-Minneapolis	9.40	-0-	9.40
		-0-	32.66	32.66
	Total Travel	$ 1,907.69	$ 1,635.25	$ 3,543.94

PUBLIC HEALTH SERVICE

FINANCIAL REPORT OF EXPENDITURES - RESEARCH PERIOD GRANTS

DATE RECEIVED: FEB 1 - 1967

DATE PROCESSED BY BRS: [illegible]

1 NAME AND ADDRESS OF GRANTEE INSTITUTION

University of Maryland
Finance and Business
660 West Redwood Street
Baltimore, Maryland 21201

2 GRANT NUMBER: PHS AM 05576-04 (KT-V541)

3 PROJECT PERIOD: FROM 9/1/64 TO 8/31/67

4 PERIOD COVERED BY THIS REPORT: FROM 9/1/66 TO 8/31/67

FUNDS AUTHORIZED FOR EXPENDITURE FOR THIS BUDGET PERIOD	
PHS FUNDS AWARDED FOR THIS BUDGET PERIOD	$ 97,805.00
BALANCE CARRIED FORWARD FROM PREVIOUS BUDGET PERIOD(S)	$ -0-
TOTAL AUTHORIZED FOR EXPENDITURE FOR THIS BUDGET PERIOD →	$ 97,805.00

EXPENDITURES FOR THIS BUDGET PERIOD — CATEGORIES		Enter TOTALS from attached schedules
PERSONNEL		$ 53,098.01
CONSULTANT SERVICES		8,200.00
EQUIPMENT		550.89
SUPPLIES		12,771.51
TRAVEL	DOMESTIC $	2,247.55
	FOREIGN $	
HOSPITALIZATION	INPATIENT $	-0-
	OUTPATIENT $	
ALTERATIONS & RENOVATIONS		-0-
PUBLICATION COSTS		798.62
OTHER		3,078.59
TOTAL DIRECT EXPENDITURES 4/65 Adj. 4233 Paid		$ 81,504.17
INDIRECT COSTS CLAIMED (Calculated at 20 % of D.C. base) 81,504.17		$ 16,300.83
TOTAL EXPENDITURES (Sum of items a) and b)) →		$ 97,805.00
BALANCE END OF THIS BUDGET PERIOD (Item 5C minus 6d) →		$ -0-
INTEREST EARNED ON PHS FUNDS (Not required for Research Grants)	$	

I hereby certify that this report is true and correct to the best of my knowledge and belief and that all expenditures reported herein have been made in accordance with the appropriate PHS grant policies and terms and conditions set forth in the application and award document.

8 NAME AND TITLE OF PRINCIPAL INVESTIGATOR — SIGNATURE — DATE

Christian Klint — 1/26/67

9 NAME AND TITLE OF GRANTEE INSTITUTION'S BUSINESS OFFICER — SIGNATURE — DATE

K. Kohlstedt, Asst. Budget Officer — K K Kohlstedt — 1/24/67

3 - INSTITUTE/DIVISION ONLY

E. Expenditures For Travel

Date of Travel	Name of Traveler and Destination	Amount
9/9-9/10/65	David P. Wilson; Phila. Pa.	$ 61.80
9/9-9/10/65	Curtis L. Meinert; Phila. Pa.	12.00
9/25/65	Christian R. Klimt; Bethesda, Md.	10.00
9/28-9/30/65	Jacob E. Bearman; St. Louis, Mo.	121.71
9/28-9/30/65	Christian R. Klimt; St. Louis, Mo.	154.24
9/28-9/30/65	Curtis L. Meinert; St. Louis, Mo.	139.86
9/28-9/30/65	Irwin P. Ho; St. Louis, Mo.	143.36
9/28-9/30/65	Phillip D. Wilson; St. Louis, Mo.	144.76
9/28-9/30/65	Beatriz R. Boschetti; St. Louis, Mo.	127.39
10/5-10/8/65	Charles O. Tack; N. Y., N. Y.	133.75
11/26/65	Wallace J. McKeel; Boston, Mass. to Balto., Md.	66.00
11/27-11/28/65	Alan S. Freemond; Cincinnati to Balto., Md. to Cinn., Ohio	98.90
1/4-1/6/66	Curtis L. Meinert; Cleveland, Ohio to Balto., Md.	40.70
1/5-1/6/66	Christian R. Klimt; San Juan, P. R.	180.15
~~1/29-1/22/65~~	~~Christian R. Klimt; [illegible]~~	~~86.00~~
2/3/66	Robert Osborne Boston, Mass. to Balto., Md. to Boston	61.60
2/19-2/20/66	Christian R. Klimt; Minn., Minnesota	42.00
3/23/66-3/26/66	Curtis L. Meinert; Houston, Texas	230.60
4/27/66-4/28/66	Henry Blackburn; Minn. to Cleveland to Minn., Minnesota	103.58
4/27/66-4/29/66	Curtis L. Meinert; Cleveland, Ohio	65.45
6/24/66	Curtis L. Meinert; Chicago, Ill.	90.10
6/22-6/24/66	Christian Klimt; Chicago, Ill.	147.60
		2216.55
12/69-3/31/66	Local Travel -$4.40; 12.80; 1.00; 12.80	31.00
	TOTAL TRAVEL	$ 2247.55

TOTAL

EXHIBIT D

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE

INSTITUTE OF INTERNATIONAL MEDICINE
BALTIMORE, MARYLAND 21201

DIVISION OF EPIDEMIOLOGY AND BIOSTATISTICS

December 14, 1967

January 2, 1968

Department of Health, Education and Welfare
Food and Drug Administration
Bureau of Medicine

Dear Doctor Finkel:

Enclosed please find my application for investigational exemption (Form 1571) for phenformin and tolbutamide used in a study known as the University Group Diabetes Program. Also enclosed please find the following:

1) Letters from the Upjohn Company and USV Pharmaceutical Company permitting cross reference to their material on file with you. In the case of DBI-TD this reference is to NDA #12-752, and in the case of tolbutamide it is File No. NDA 10-670.

2) Three copies of the protocol of the University Group Diabetes Program.

3) Three copies each of Form 1573 from the twelve principal clinical investigators.

4) One copy of our major progress report, prepared in 1966.

5) One copy of our most recent progress report, October 1967.

6) A set of labels known as sealed tear off labels as used in the University Group Diabetes Program.

7) A copy of our form documenting written patient consent.

As you are aware the University Group Diabetes Program has been in operation since September 1960 and has just now been renewed by NIH National Institute of Arthritis and Metabolic Diseases for a period up to seven years. Since January 1966 no new patients have been added to the study and the number of active patients, which at its peak was 1,023, has dropped to 852 active patients by the end of November 1967.

The study will again be reviewed in 1970 by NIH and an independent review committee to decide how long this study should continue. The major report will be prepared by counsel (?) for this review. In the interim, relatively brief reports are being submitted annually at the time of grant renewal in May of each year. (COPY NOT CLEAR COPY NOT CLEAR — COPY NOT CLEAR — COPY NOT CLEAR). I can be reached directly by telephone at the following number, A.C. 301-727-7184.

Yours sincerely,

/s/ Christian R. Klimt, M.D., Dr. P.H.
Christian R. Klimt, M.D., Dr. P.H.
Professor and Director

CRK:bbb

enc

cc: All Principal Investigators, UGDP
Dr. Rosemarie Petrucelli, NIAMD
Dr. Keith Borden, Upjohn Co.
Dr. Hans Keitel, USVP Co.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

Peter H. Forsham, et al., *Plaintiffs*

v.

David Mathews, et al., *Defendants*

AFFIDAVIT OF CHRISTIAN R. KLIMT IN SUPPORT OF MOTION TO DISMISS AND TO QUASH SERVICE OF PROCESS

City of Baltimore
State of Maryland, ss

Christian R. Klimt, M.D., Dr. P. H., being first duly sworn deposes and says:

1. I am a Professor in the Department of Social and Preventive Medicine at the University of Maryland School of Medicine, and am Director of that Department's Division of Clinical Investigation. As principal investigator under grants to the University of Maryland from the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), one of the institutes of the National Institutes of Health (NIH), headquartered in Bethesda, Maryland, I am Director of the Coordinating Center of the University Group Diabetes Program (UGDP).

2. Prior to becoming principal investigator under the NIAMDD grants to the University of Maryland, I was principal investigator under similar grants to the University of Minnesota. I have been Director of the Coordinating Center for UGDP since its inception in 1960.

3. The Coordinating Center is presently located at 600 Wyndhurst Avenue, Baltimore, Maryland. At no time has the Coordinating Center been located in Washington, D.C.

4. As Director of the Coordinating Center and principal investigator under the NIAMDD grants, I have filed numerous applications and reports with NIH, which as previously noted is headquartered in Bethesda, Maryland, and with the Food and Drug Administration (FDA), Bureau of Drugs, now headquartered in Rockville, Maryland, and previously in Arlington, Virginia. I have also conducted correspondence with these same agencies concerning UGDP matters. To the best of my knowledge, information, and belief, I have never corresponded with anyone on UGDP matters at the headquarters of the United States Department of Health, Education, and Welfare in Washington, D.C. Exhibit D to Plaintiffs' Memorandum in Opposition to Defendant's Motion to Dismiss and to Quash Service of Process, being a letter to Dr. Marion J. Finkel dated December 14, 1967 and January 2, 1968, was misaddressed, since Dr. Finkel was Director of the Division of Metabolism and Endocrine Drugs of the Bureau of Medicine (now the Bureau of Drugs), and her office address was Crystal Palace, Arlington, Virginia.

5. Plaintiffs' Exhibit C to their Memorandum in Opposition to Defendant's Motion to Dismiss and to Quash Service of Process refers to certain UGDP travel expenditures and lists travel to Washington, D.C. on certain dates. I have checked my personal calendars which indicate that on dates highlighted by Plaintiffs which list Washington, D.C. as my destination, I was actually only in Washington, D.C. proper on UGDP matters twice, and for the following reasons:

11/12/64—Appointment with a cardiac specialist at George Washington University

01/19/66—American Diabetes Association Meeting, Post-Graduate Course in Washington, D.C. at the Mayflower Hotel, to give a lecture entitled, "Epidemiology of Diabetes," and to chair the ADA Statistical Committee Meeting.

The remaining dates which list Washington, D.C. as the destinations actually refer either to Bethesda, Maryland, where NIH is headquartered, or to stops in Washington, D.C. while in transit to other locations, or to National Airport, in Virginia. I have used the designation "Washington, D.C." interchangeably with Bethesda, Maryland, and National Airport, in Virginia, when I have itemized expense statements as I have considered each to be in the Washington, D.C. metropolitan area for mileage allowance purposes.

/s/ CHRISTIAN R. KLIMT, M.D., Dr. P.H.
Christian R. Klimt, M.D., Dr. P.H.

Subscribed and sworn to before me this 4th day of December, 1975.

/s/ VIRGINIA ? ? ? ?
Notary Public

My Commissions Expires: July 1, 1978.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, *et al., Plaintiffs,*

v.

DAVID MATHEWS, *et al., Defendants.*

MOTION TO DISMISS OR IN THE ALTERNATIVE FOR SUMMARY JUDGMENT ON BEHALF OF THE FEDERAL DEFENDANTS

Original Filed Nov. 21, 1975

The federal defendants, the Secretary and Assistant Secretary of the Department of Health, Education and Welfare, the Commissioner of the Food and Drug Administration, and the Director of the National Institute of Arthritis, Metabolism, and Digestive Disease, through their attorney, the United States Attorney for the District of Columbia, respectfully move the Court to dismiss this action for failure of the complaint to state a claim upon which relief can be granted. Rule 12(b)(6), Federal Rules of Civil Procedure.

Alternatively, defendants respectfully move the Court to grant summary judgment in their favor on the ground that no genuine issue exists as to any material fact and they are entitled to judgment as a matter of law. Rule 56, Federal Rules of Civil Procedure.

In support of the motion, defendants submit herewith a statement of material facts, a memorandum of points and authorities, and the following exhibits:

Fed. Defs. Exhibit 1—Affidavit of Theodore Cooper, M.D., Assistant Secretary for Health, Department of

Health, Education and Welfare, with attached certified documents.

Fed. Defs. Exhibit 2—Public Information Regulation, Department of Health, Education and Welfare, August 1974.

Fed. Defs. Exhibit 3—Affidavit of G. Donald Whedon, M.D., Director of the National Institute of Arthritis, Metabolism and Digestive Diseases.

Defendants also submit herewith a proposed Order.

EARL J. SILBERT
United States Attorney

ROBERT N. FORD
Assistant United States Attorney

JULIUS A. JOHNSON
Assistant United States Attorney

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, *et al., Plaintiff,*

v.

DAVID MATHEWS, *et al., Defendant.*

AFFIDAVIT

City of Washington)
District of Columbia) ss:

Theodore Cooper, M.D., being first duly sworn, deposes and says:

1. I am the Assistant Secretary for Health, United States Department of Health, Education and Welfare. In that capacity, I coordinate the health and health-related functions of the Department and I direct the activities of the Public Health Service, which includes the Food and Drug Administration and the National Institutes of Health.

2. I am a defendant in the above-entitled matter and have read, and am familiar with, the plaintiffs' complaint.

3. As the Assistant Secretary for Health, I have authority to act on requests for review from a person who has requested records of the Public Health Service under the Freedom of Information Act and whose request has been denied in whole or in part. This authority is stated in the Department of Health, Education and Welfare Public Information Regulation, 45 CFR 5.4 and 5.82. My action on a request for review of such records constitutes final agency action.

4. I have been advised, and so state on information and belief, that Mr. Neil Chayet, on behalf of the plaintiffs, made a request under the Freedom of Information Act by letter, dated November 4, 1974, addressed to Mr. Peter Barton Hutt, then the Assistant General Counsel Food and Drug Division, for a copy of a draft report of the Biometic Society on its study of the conclusions of the University Group Diabetics Program and for the raw data upon which the report was based. (A copy of that letter is attached hereto as appendix A).

5. I am advised, and so state on information and belief, that the Department's Freedom of Information Officer denied access to the draft report on the basis that it was a draft and that the final report would be released. (A copy of the letter of the Freedom of Information Officer is attached hereto as appendix B).

6. I am advised, and so state on information and belief, that Mr. Chayet, on behalf of the plaintiffs, appealed to my predecessor, Dr. Charles C. Edwards, the denial of access to the draft report and the apparent denial of the raw data upon which the report was based. (A copy of Mr. Chayet's letter dated January 2, 1975, is attached hereto as appendix C). In response thereto, Mr. Chayet was provided with a copy of the draft report which had been provided to the Director National Institutes of Arthritis, Metabolism and Digestive Diseases (NIAMDD) National Institutes of Health, and which was published in the February 10, 1975 issue of the Journal of the American Medical Association. Mr. Chayet was also advised that no one in the Department had any of the raw data upon which the report was based. (A copy of the letter of the Director, NIAMDD, to Mr. Chayet dated January 27, 1975, is attached hereto as appendix D).

7. By letter dated May 6, 1975, (a copy of which is attached hereto as appendix E) Mr. Chayet appealed to me as Acting Assistant Secretary for Health stating that he had

not in fact been provided with a draft copy of the Biometrics Society report as he requested. He also "renewed" appeal for the raw data upon which report was based.

8. I replied by letter dated May 23, 1975, (a copy of which is attached hereto as appendix F) advising Mr. Chayet that the copy of the report furnished to him was the draft report and the only one provided to the Public Health Service. I also advised Mr. Chayet that no officer or employee had ever had any of the raw data collected by the University Group Diabetes Program and that, since that data did not constitute records of the Department of Health, Education and Welfare, I could not provide access to or copies of it to him.

9. By return letter dated June 3, 1975, (a copy of which is attached hereto as appendix G) Mr. Chayet asserted that since the University Group Diabetes Project was funded with Federal funds through a grant from the National Institutes of Health, the Department of Health, Education and Welfare should request it from the grantee in order to provide it to a requestor under the Freedom of Information Act.

10. I replied to Mr. Chayet by letter dated June 24, 1975 (a copy of which is attached hereto as appendix H) that the raw data he requested was not part of a record of this Department and could not, in my opinion, be considered even in the constructive possession of the Department).

11. By letter dated July 8, 1975 (a copy of which is attached hereto as appendix I) Mr. Chayet took exception to my statements in my letter of June 24, 1975.

12. By letter of August 7, 1975 (a copy of which is attached hereto as appendix J) I further advised Mr. Chayet that no official of the National Institutes of Health or Food and Drug Administration had ever had the raw data relating to the University Group Diabetes Program study. I further advised that it is not the practice for the National

Institutes of Health to require grantees to submit their raw data for review and that no specific provision of either the University Group grant or the Biometrics Society contract required submission of raw data to the Department of Health, Education and Welfare. I concluded that the raw data is the property of the individual investigators and the coordinating center and that the Department has no authority to order that the data be made available to Mr. Chayet or his clients.

13. Officials of the National Institutes of Health and I have cooperated with Mr. Chayet to the fullest extent possible. Mr. Chayet's law firm on behalf of his clients, has been permitted access to the entire file of the National Institute of Arthritis, Metabolism and Digestive Diseases, concerning the University Group study and, with the exception of the raw data which is the subject of this case, has been provided copies of all records requested except for data pertaining to salaries of individuals named in grant applications and portions of documents containing opinions of cosultants serving as members of the initial review group who reviewed the grant applications prior to funding of the grants. Mr. Chayet has not appealed the withholding of the latter information.

14. As I have advised Mr. Chayet, the raw data he seeks on behalf of the plaintiffs is not contained in records of the Department of Health, Education and Welfare and to my knowledge has never been in the possession of any officer or employee of the Department.

15. The University Group Diabetes Study was begun in 1961 and has studied over 800 patients over a period of ten years in 12 university medical school clinics. This study is the largest controlled clinical trial of oral oglycenic agents to date and has been supported by grants from the National Institute of Arthritis, Metabolism and Digestive Diseases. Following publication of the results of the study in 1970, the preliminary results of other studies appeared

to differ. In order to assess the scientific quality of the University Group study, in particular the biometric aspects of the design, conduct and analysis of the trial as well as other trials of oral hypoglycemic agents the Director of the National Institutes of Health invited the President of the Biometrics Society to appoint a committee to consider the biometric aspects of controlled trials of oral hypoglycemic agents. The Biometric Society is a non-Governmental organization of scientists. The work of the committee selected to conduct the study was supported by a contract with the National Institute of Arthritis, Metabolism and Digestive Diseases. The Committee's report on that study is the report referred to in paragraphs 4, 5 and 6, above.

/s/ THEODORE COOPER
Theodore Cooper, M.D.
Assistant Secretary for Health

Subscribed and sworn to before me, a notary public, in and for the District of Columbia this 10th day of Oct., 1975.

/s/ Signature Illegible
Notary Public

My Commission Expires July 31, 1976.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, et al., *Plaintiff*

v.

DAVID MATHEWS, et al., *Defendants*

AFFIDAVIT

County of Montgomery)
State of Maryland)

G. Donald Whedon, M.D., being first duly sworn, deposes and says:

1. I am Director of the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD), one of the Institutes of the National Institutes of Health, (NIH), Department of Health, Education and Welfare, Bethesda, Maryland. My curriculum vitae is attached as Exhibit 1.

2. This Institute (NIAMDD), with the advice of a number of peer review committees of distinguished and highly knowledgeable scientists, is responsible for reviewing and administering research grants and contracts in the areas of arthritis and metabolic diseases in numerous university centers, research institutions and teaching hospitals throughout the United States. Support of research in the field of diabetes is a particular responsibility of NIAMDD.

3. In my position, I have, together with my colleagues, had ample opportunity to review the inception, planning, conduct and conclusions to date of a study known as the University Group Diabetes Program (UGDP). The UGDP was a long-term prospective, controlled study, undertaken in 1961 at 12 cooperating clinics to determine the incidence and development of degenerative complications of diabetes mellitus. The study was conducted in patients with newly

diagnosed, maturity-onset diabetes. Initially, the UGDP study involved four treatment regimens: (1) diet alone; (2) diet plus insulin in standard dose; (3) diet plus insulin in variable dose; and, (4) diet plus tolbutamide. In 1963 a fifth regimen was added: diet plus phenformin. Approximately 1,027 patients participated in the study, (200 per treatment group). The patients were monitored for from five to eight years.

4. The inspiration for the UGDP study came from private non-government physicians and scientists in mid-1959. Between 1959 and 1961, before the study actually began with the entry of the first patients, the design, methods, and objectives of the study were evaluated by persons associated with the UGDP and representatives of NIAMDD. The Food and Drug Administration was not involved in the planning, inception, or design of the UGDP study. The study was funded by NIAMDD as part of its responsibility to support research in the field of diabetes and not with any specific regulatory objective in mind.

5. The UGDP has been and still is funded by 13 grants from this Institute. A copy of the Coordinating Center grant and a grant for one of the 12 clinics are attached as Exhibits 2 and 3 respectively. Applications from the Coordinating Center and the 12 participating clinics of the UGDP were received and reviewed by a special review committee of NIAMDD during 1960-63 that recommended approval on the basis of merit. The UGDP was also recommended by the National Advisory Arthritis and Metabolic Diseases Council at its meetings in June, 1960, June, 1961, June, 1962, and June, 1963. The Council provided the recommendations for approval necessary by law for funding of the research by NIAMDD.

6. The 13 research grants of the UGDP came up for consideration of renewal for continuation of the study in 1966. They were first reviewed by a Special Study Section (a panel of experts in diabetes research and treatment) of

NIH in September 1966 and by the National Advisory Arthritis and Metabolic Diseases Council in November 1966. After careful analysis and discussion, both groups recommended approval. Support of the study by NIAMDD continued.

7. The 13 grants again came up for review in 1971. A Special Study Section of NIH met in July and, on the basis of merit, again recommended approval. The Council, at its meeting in November 1971, also recommended approval and rated the UGDP study of "High Program Relevance". This rating was, in effect, a direction to Institute staff to provide financial support for the UGDP grants regardless of the competition of other applications for funds available for research grants.

8. Continuing studies by the cooperating clinics and analysis of the data by the Coordinating Center will be supported until August 31, 1977.

9. The UGDP raw data (e.g., patient charts and forms) are the property of the individual investigators and the Coordinating Center and are not owned by NIAMDD. Furthermore, it is not the normal practice of NIH or this Institute to require grantees to submit their raw data for review and, in fact, submission of raw data to the institute is extremely rare. Management of the day-to-day operations of grant-supported activities is the responsibility of the grantee. Supervision of the grantee's funded activities by this Institute is generally limited to review of periodic reports submitted by the grantee. (45 CFR §§ 74.80, 74.82). Due to the large number of research grants outstanding—currently approximately 1800—it would not be physically possible for the Institute to subject raw data, if submitted, to critical review, and to require submission of the raw data of the UGDP study would have been an extraordinary requirement. It is the practice to evaluate applications for renewal grants on the basis of progress reports and final reports submitted to NIH. This practice was followed with respect to the UGDP grants. No specific provision of the

UGDP grants required submission of raw data to the Department of Health, Education, and Welfare. Pursuant to 45 CFR § 74.23, officers or employees of the Department could obtain access to the raw data for purposes of audit inspection and copying if access is deemed pertinent to the grant. The raw data which are the subject of this case have never been seen by, or been in the possession of, any officer or employee of the National Institutes of Health. I have been advised, and on information and belief so state, that the documents comprising the raw data currently number in the millions, possibly as many as 55 million, and contain information that would identify the patients.

10. The National Institute of Arthritis, Metabolism, and Digestive Diseases supported by contract a study of the biometric aspects of the design, conduct and analysis of the trial of the University Group Diabetes Program as well as other trials of oral hypoglycemic agents. This study of the biometric aspects of these trials was conducted by a committee of the Biometric Society, a private professional society. The contract did not require either that the committee seek access to the raw data or that any raw data that may be studied be transmitted to the Institute. At the conclusion of the study, the committee did not submit to the Institute any raw data pertaining to the University Group Diabetes Program, or any other raw data. The results of the committee study were published in the Journal of the American Medical Association.

/s/ G. Donald Whedon
G. Donald Whedon, M.D.

Subscribed and sworn to before me, a Notary Public, in and for the State of Maryland this 18th day of November, 1975.

/s/ Sally A. Linn
Sally A. Linn
Notary Public

My commission expires July 1, 1975.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

Peter H. Forsham, Henry Dolger, Holbrook S. Seltzer, as they are members of the Committee on the Care of the Diabetic, *Plaintiffs*,

v.

David Mathews, Secretary of the Department of Health, Education, and Welfare; Theodore Cooper, Assistant Secretary of Health, Department of Health, Education and Welfare; Alexander M. Schmidt, Commissioner of the Food and Drug Administration. G. Donald Whedon, Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases; Christian R. Klimt, *Defendants*.

PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

Now come plaintiffs in the above-entitled action and oppose the Government defendants' Motion to Dismiss or In The Alternative for Summary Judgment and offer in support thereof the Memorandum of Points and Authorities accompanying plaintiffs' Complaint filed September 30, 1975 (See in particular, pages 19-25); and the Memorandum of Points and Authorities submitted herewith.

Plaintiffs respectfully request a hearing on this Motion.

Respectfully submitted,

CHAYET AND SONNENREICH, P.C.

By:

NEIL L. CHAYET

HARVEY W. FREISHTAT

Attorneys for Plaintiffs
Six Fayette Street
Boston, Massachusetts 02116

Telephone No.: (617) 357-0202

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, *et al.*, *Plaintiffs*

v.

DAVID MATHEWS, *et al.*, *Defendants*

MOTION FOR SUMMARY JUDGMENT

Plaintiffs in the above-captioned matter respectfully move the Court to grant summary judgment in their favor on the grounds that no issue of material fact exists and they are entitled to judgment as a matter of law. Rule 56, Federal Rules of Civil Procedure.

In support of their motion for summary judgment and in opposition to defendants' motion to dismiss and for summary judgment, plaintiffs submit herewith a memorandum of points and authorities and exhibits.

Plaintiffs respectfully request a hearing on the within Motion.

Respectfully submitted,

CHAYET AND SONNENREICH, P.C.

By:

NEIL L. CHAYET

HARVEY W. FREISHTAT

Attorneys for Plaintiffs
Six Fayette Street
Boston, Massachusetts 02116

Telephone No.: (617) 357-0202

EXHIBIT A

STATEMENT OF

ANGELA J. BOWEN, M.D.

BEFORE

THE FOOD AND DRUG ADMINISTRATION
PUBLIC HEARING ON THE PROPOSED LABELING
FOR ORAL HYPOGLYCEMIC DRUGS

AUGUST 20, 1975

My name is Angela Bowen. I practice medicine in Olympia, Washington. I am a reluctant witness here today because what I must say will complicate the lives of old friends and acquaintances. I have tried to avoid active participation in the controversy because I still number many of the investigators of the UGDP among my closest friends. My association with the UGDP began in 1963 and continued until 1970 when I resigned for reasons that will become apparent shortly.

The results of the study have been subjected to a variety of criticisms, usually on the scientific merit. If one were to judge the study simply on its published claims a seasoned investigator would marvel at how everything was done *exactly* as planned in the protocol. Most investigators will acknowledge that the final performance of a research project rarely approximates the initial plan, however well thought out. As a long time participant in the UGDP I can assure you that it didn't happen that way in this study either. I am refering now to the day to day conduct of the study.

This was unremittingly dull work and tended to be assigned to the most junior member of the pecking order, a position in which I found myself in those days. I therefore became well acquainted with the day to day drudge involved in such a study. It is the accurate performance of this daily drudge that holds the key to the strength or weakness of such a study. There were of course wide differences in its

performance in the different clinics. It was almost never done by the principal investigator, sometimes by third year medical students, sometimes by residents or other temporary personnel. Thus, differences in the maturity and quality of clinical judgment were apparent in evaluation of complications and side effects.

Certainly there was an honest attempt by the Principal Investigator to initially do everything by the book. But, as the tasks became shunted to the periphery, enthusiasm waned. Gathering of data was complicated by the long term nature of the study and the fact that six of the original twelve investigators left and were replaced at various points in the study. I have serious doubts as to the accuracy with which the data was collected in the various clinics.

For example, most investigators had a bias that control of blood sugar was not important. Some investigators were thus willing to let blood sugar levels get quite high without intervening with alternate treatment. Our group, on the other hand, felt that a normal blood sugar level was preferable to an abnormal one and we tended to prescribe alternate treatment fairly early if the study medication did not do the job—thus, our clinic had a fairly high number of people who were taken off study medication and managed by usual and customary means.

This may explain why the death rate was much lower at our center. These are just a few examples of problems I observed in the day to day conduct of the study. There are others.

An even more troublesome aspect has not been as well explored. This involves the matter of personal integrity and scientific honesty of one key member of the group. This question was actively considered both privately and openly among the investigators as early as 1968. It has also been asked publicly since that time. The question that the FDA must now ask and hopefully answer is "were the data that were gathered in the field accurately and honestly

recorded and reported from the coordinating center in Baltimore?" I fully recognize that this is a serious allegation but there is basis for reasonable doubt. You will recall that this was a double blind study. Invesitigators did not know what medication a paient was taking. Data were simply recorded and sent along to the biostatistician at the coordinating center. We then received a printout of the cumulative results. Therefore if one was told that a given death or side effect occurred in a tolbutamide patient it was taken on faith because the investigator never knew for sure. It did not occur to me to question this state of affairs until 1968 when the first allegation was made that the death rate was higher in the tolbutamide group. At the same meeting another investigator revealed that the biostatistician, Dr. Klimt, was a paid consultant to U.S. Vitamin, the then makers of phenformin. This was at first denied, then acknowledged. A spirited discussion followed during which the potential for abuse under such circumstance was discussed at length. This ended with the demand from the New York delegates that an independent review of the data be undertaken by outside statisticians. Dr. Klimt threatened to resign if this was done. This threat did not meet with universal disapproval, but a compromise was finally reached in which a review would be done but Dr. Klimt would be permitted to choose the reviewers! Drs. Cornfeld and Brown were his choices. It is my understanding that they simply reviewed the numbers and methods sent to them by the coordinating center and that raw data were not used even then. This episode caused a rift of major proportions among the investigators.

The situation was not improved when the Phenformin data continued to be unavailable. The reason was given that the coordinating center was overworked, the computer wasn't working well and finally that insufficient time had elapsed. These may have been valid reasons, but—they simply did nothing to reassure the skeptics among us that no collusion existed between USV and Dr. Klimt. As you

may have gathered, the UGDP was, for me, a very disillusioning experience.

As this matter progressed, it became increasingly difficult to voice legitimate scientific concerns, and the entire project began to assume a vendetta-like quality against the manufacturer of tolbutamide. For example, when the attached list of patients (See attachment A) was provided by Dr. Kenneth Kreins of Cincinnati to illustrate his anxiety that the patients in the tolbutamide treatment group were very ill from causes not related to their diabetes, he was interrupted by the Chairman (Thaddeus Prout, M.D.) and not permitted to proceed.

Several subsequent meetings were held where this matter was discussed. The meeting at Jamestown during the following year led to a vote being taken about whether the evidence was strong enough to warrant discontinuing tolbutamide. Again the investigators were divided. There were demands by the program chairman (Dr. Max Miller) that complete unanimty be reached because otherwise the decision would not be viewed as seriously as he hoped it would be. This meeting was committed to tape in its entirety and will corroborate that feelings continued to run strong that dishonesty was a real possibility. My co-investigator requested from the coordinating center a printout of the data from our clinic to determine whether it agreed with our own data kept in the clinic. That request, like all other requests, was refused. The jealousy with which access to the data has been guarded to all who requested it is not reassuring. Dr. Reeves, my co-investigator, and I felt that we could not in good conscience attach our names to the conclusions proposed and finally released by the UGDP. We therefore resigned rather than do so. A year or so later the phenformin data became available and there was pressure from some investigators to drop it too. A representative from USV came to Olympia and alleged that he had been told by Dr. Klimt that we were told people who were most interested in seeing that phenformin was dropped from the study.

We, of course, no longer were involved in the study and certainly no voice in what was done about phenformin. One can only speculate why such charge might have been made by Dr. Klimt if in fact, it was made. This episode permanently fix in my mind the strong suspicion that a continuing relationship existed between USV and Dr. Klimt.

It is not my intent to make statisticians sound less honest than the rest of us. Unfortunately their language is not spoken by the many who must live by their decisions. It is possible that no dishonesty existed. It is equally possible that it did. But, since the FDA has assumed the role of final arbiter in this issue, the FDA should know for sure. It is unfortunate that the agency assumed the position of supporting the UGDP conclusions prior to their full scientific review. This has given the illusion of rigidity and some have suggested that Dr. Klimt was instrumental in this approval since he was also working here at the FDA when that approval was given. These are simply troublesome questions that nag at some of us and I would be very happy if they could be explored and proven to be groundless. The cloud surrounding this study must now either be dispelled or confirmed. Those of us who live in the provinces and work on the front lines of patient care have come in recent years to feel somewhat abandoned by the FDA. It has appeared more and more to be taking the position that practicing physicians are not to be trusted with medications or pharmacologic decisions and that these decisions are best made by the Commissioner and transmitted directly to the patient via the wire services. Now this may not actually be the position of the agency but it is how it is perceived in the field.

What of the patient? How does he fare when decisions are made regarding his therapy by some distant committee of experts? I have pulled from my files the case of one such patient and could have brought a dozen others, to illustrate what can happen under such circumstances. This patient was one of the UGDP patients from the Seattle clinic who

had been treated with Phenformin and was switched to placebo when Phenformin was discontinued from the study. She came down to Olympia requesting treatment, bringing with her letters from the investigator showing that her blood sugar had steadily increased from 133 fasting to 321 after being managed with diet and placebo. Although she had protested that her skin was covered with a rash, she was developing dupuytrens contractures and had no energy to go about her daily tasks, she had been refused treatment. I prescribed treatment and her symptoms cleared straightaway. She again returned to the research clinic and was again put on placebo. Some months later she reappeared at my office with the same symptoms and a blood sugar of 289. I prescribed one of the oral agents and received in a few weeks the following letter:

(See Attachment B)

This demonstrates the numerous complications that come with aberrations in the blood sugar level that are not life threatening but certainly affect the patient's condition. Any practicing physician would have treated her as I did.

A few months ago I was privileged to hear one of the UGDP's principal investigators present data from a study of Glyburide. His last slide indicated what treatment the patients were transferred to when the Glyburide study was finished. Almost every patient was placed on oral agents. I could not, of course, resist public comment on his lack of faith in the UGDP conclusions, as evidenced by his clinical actions. After a few moments of silence he replied that, "yes he did have misgivings about the result" and that he believed normal blood sugars were preferable to abnormal ones and he planned to continue using oral agents.

What then are my recommendations to the FDA? I would like to see the Agency approach this exactly as they would if Upjohn or Ciba-Geigy or Pfizer came in claiming that their drugs prevented heart disease. You would demand proof and good quality case reports accurately reviewed.

The same should be done here. If there was the slightest indication that a clinical investigator had manipulted data to the drug company's benefit you would send an auditor to the scene and scrutinize the operation. That should be done here. Every case report in every clinic should be reviewed. The FDA must be above reproach.

If scientific issues are going to be discussed in the package insert, both sides should be presented, preferably as literature references and not as summaries prepared by the Agency. Dr. Simmons had said in communications to us that to present both sides of a controversy would "hopelessly confuse the practicing physician." Well, hopeless confusion is no stranger to the average practicing physician, she knows it well. I would then, like to see a little humility when these issues directly affect patient care as they do in this case. I would like to see fair balance in the package insert. The package insert seems a curious place to make alternative treatment suggestions. It is, you know, almost never seen by the physician. The pharmacist is usually the one who discards it unread into his basket. The suggestion that Insulin is the treatment of choice in this group of diabetics usually treated with oral agents is one that defy's understanding. Such an experiment hasn't been done that showed any benefit to the patients longevity.

As long as the practice of medicine has exicted the physician has had the right to select what he considers the proper therapy for the individual patient based on the most widely accepted scientific information available. Patients rely on their physicians for such advice. It is my fear, and that of many others that this important right is seriously threatened.

I fully understand how much courage it would require for the FDA to change its position on the UGDP at this late date, but I insist upon believing that it is capable of doing so if the evidence is compelling.

#50015 - J

This patient had severe generalized large vascular disease with previous strokes, myocardial infarctions and peripheral vascular insufficiency. One and one half years prior to death he was transferred to a chronic disease hospital and was lost to follow-up until five days prior to his death on 11/2/66. He claimed to have continued to take his AB medications, but this is doubtful. AB Rx was restarted, but the following day the patient was admitted to another hospital with bilateral flaccid paralysis, Cheyne-Stokes respirations and dysphagia and succumbed on 11/7/66 from presumed basilar artery thrombosis. I spoke with the attending physician and feel that the diagnosis is probably correct. During the terminal hospitalization the patient was receiving known tolbutamide.

#50017 - F

This patient with hypertensive and arteriosclerotic cardiovascular disease and angina pectoris was last seen in the UGDP Clinic on 5/26/65. He was admitted to the Cincinnati General Hospital on 5/30/65 with a cerebral infarct. Pneumonia supervened and the patient expired on 6/27/65. Autopsy revealed a fresh myocardial infarction, presumably the terminal event. During hospitalization AB treatment was discontinued and insulin substituted.

#50069 - L

This patient had known severe arteriosclerotic heart disease with angina pectoris and congestive heart failure. Three weeks prior to death chest x-rays revealed cardiomegaly and pulmonary congestion. Patient died in the emergency room at Cincinnati General Hospital on 8/22/66 with severe pulmonary edema. Although an electrocardiogram was not taken, the pulse rate was 140/minute rendering arrhythmia an unlikely diagnosis.

#50033 - M

This patient was admitted to the Cincinnati General Hospital thirteen days prior to death because of hemiparesis. Angiograms revealed an aneurysm of the right internal carotid artery. Chest x-rays revealed a small left plural effusion, possibly due to pulmonary embolus. The patient expired suddenly on 2/10/66. The immediate cause of death may have been rupture of the demonstrated aneurysm, cerebral thrombosis or pulmonary embolism.

#50008 - M

This patient with long standing aortic stenosis previously suffered a left-sided CVI presumably due to cerebral embolism. Recovery was complete except for seizures for which she took dilantin. She was admitted to the hospital on 3/11/64 with severe dysphagia and dysarthia and died the following day. Post mortem revealed calcific aortic stenosis, old myocardial infarction, mural thrombus, pneumonia and fresh embolization to a kidney. The probably cause of death was cerebral embolus. The brain was examined but the report cannot be found.

#50089 - F & C

Died of perforation of the gall bladder on 10/16/66. No evidence of cardiovascular disease. Good adherence.

#50041 - V 1 F

Died 1/7/66 at Cincinnati General Hospital of bleeding gastric carcinoma and pneumonia. When last seen in clinic on 12/8/65 patient was taking his AB Rx plus digitalis.

#50050 - M C

Died at home on 12/9/63 of metastatic carcinoma of colon. Last seen in UGDP Clinic on 9/11/63. Hospitalized at Cincinnati General Hospital on 9/27 to 10/7/63 at which time she was on known tolbutamide. No Rx after discharge.

#50037 - Goldie J

Patient with known ASHD, angina and CHF taking digitoxin, diuril and KCl, died at Cincinnati General Hospital on 11/17/64 of intestinal obstruction due to metastatic carcinoma of colon.

#50039 - Alice J

Patient became a clinic treatment failure six months after admission because of severe symptoms of hyperglycemia. Insulin treatment was attempted but patient could not administer injections. Patient took known tolbutamide 1.5 gr. daily thereafter. This patient had paresis and gradually deteriorated becoming progressively disoriented and weakened physically. Terminally, she was confined to a nursing home where she developed pneumonia. The immediate cause of death was multiple pulmonary emboli from a venus thrombosis in the left calf.

#50005 - C ie N

This patient had long standing severe ASHD with ECG changes of previous myocardial infarction and of auricular fibrillation. For several months prior to death he manifested severe congestive heart failure and was treated in the emergency room for this condition five days prior to death. He was seen in the Cardiac Clinic one day prior to death where it was noted that his prothrombin time was only 12%. The patient was receiving coumadin. The following day he was brought to the emergency room DOA. Death may have been caused by congestive heart failure, a myocardial infarction, an arrhythmia, or by a hemorrhage (cerebral or subintimal), secondary to hypoprothrombinemia.

#50026 - B

This patient had no known history of cardiovascular disease. She was seen one week prior to death at which time she complained of left sided abdominal pain, nausea and vomiting. Gastro intestinal x-rays were ordered, but she died suddenly on 10/5/67 before the x-rays could be taken. This patient had dropped out of the UGDP Clinic in August of 1963 and, to our knowledge, took no anti-diabetic medications thereafter. Cause of death is unknown.

#50016 - N H

This patient was last seen in the UGDP Clinic on 8/7/63 and died suddenly in Corbin, Kentucky on 10/30/63. Death certificate lists "heart failure", but this could not be substantiated. ECG and blood pressure were normal on 8/7/63. There was no prior evidence of cardiovascular disease. This patient took AB treatment from admission on 3/10/61 through 5/63 when she was made a treatment failure because of severe symptoms of hyperglycemia. She took 10-15 units of Lente insulin daily for the remaining five months of her life.. Cause of death is unknown.

ATTACHMENT B

Had a wonderful 3 weeks in Honolulu.

From the Desk of—W. S. Howard

Dear Angela:

I wrote Dr. Nielson—Telling him how bad I had gotten and felt I needed a change in medicine, so had transferred to a new Dr. in Port A. & would be discontinuing with the Diabetic Clinic.

This is a copy of his reply. Is he trying in the 2nd ¶ to tell me pills only keep blood sugar down and dosn't really aid diabetes? I can't believe it. I feel like a new person since I went back on Dymelor. Rash gone—hands 90% improved etc.—& I was doing fine on the DBI at the clinic.

I didn't tell him I saw you or Dr. (?) name, and I'm not answering this letter or going back. I think he would have let me die. I told him of the numbness I had, knowing from past experience it was sugar acid in the blood—Dr. Hughes told me that, But Dr. Nielson didn't say a word.

Just wondered if you agree with ¶. 2. Thank you again.

Marjorie.

VIRGINIA MASON RESEARCH CENTER

of the Virginia Mason Foundation for Medical Education and Research

1000 Seneca Street • Seattle, Washington 98101 •
MAin 4-1144, Area Code 206

January 22, 1974

Mrs. W. Seymour Howard
P.O. Box 267
Sequim, Washington 98382

Dear Mrs. Howard:

Thank you very much for your letter of January 16. As I look back over the blood sugar result we have had on you over the past several years, there has indeed been a gradual increase in the fasting levels. As you know, the study was designed to evaluate the effectiveness of various treatment programs on the progress of diabetes and, also, as you know, the study has shown that the active pills used in this study have resulted in no improvement in complication rates and, indeed, have resulted in some minor increase in death rate, as opposed to patients who were on the non-active pills. At the present time you have been on a non-active pill.

There is, to date, no evidence from the study that keeping the blood sugar normal with the pills in any way influences the progression of diabetes complications, and it was for that reason that we have continued to feel justified in not putting you on an active agent (such as the Dymelor you are now on) to bring your blood sugar back to normal.

This is a milestone study in American medicine, and it is extremely important that it be carried to completion—which should be within the next year. I would greatly appreciate, therefore, your returning to the study if you can see your way clear to do so. I realize there is a transporta-

tion problem, but we would be willing to pay your round-trip bus fare from Port Angeles for your visits every three months, and perhaps we could also arrange to make your visits at six-month intervals and combine a couple of examinations.

As you know, there are differing philosophies among physicians about the treatment of diabetes, and if your doctor is opposed to your continuing the study I would like very much to have the opportunity of communicating with him. Please let me know your present feelings and the name of your doctor so that I may write to him—provided you decide to return to the study.

Again, I would urge you that this is an extremely important study and at this point in time the dropout of even one patient is a significant deterrent to its successful completion.

Sincerely,

/s/ ROBERT L. NIELSEN
Robert L. Nielsen, M.D.

RLN:ps

FEDERAL REGISTER, VOL. 39, NO. 248—
TUESDAY, DECEMBER 24, 1974

§ 4.101 Administrative enforcement records.

(a) All Food and Drug Administration records relating to administrative enforcement action disclosed to any member of the public, including the person who is the subject of such action, are available for public disclosure at the time such disclosure is first made. Such records include correspondence with companies following factory inspection, recall or detention requests, notice of refusal of admission of an imported product, regulatory letters, information letters, Forms FD-483 and FD-2275 furnished to companies after factory inspection, and similar records.

(b) To the extent that any of such records fall within the exemption for investigatory records established in § 4.64, the Commissioner determines that they are subject to discretionary release pursuant to § 4.82.

(c) Records relating to administrative enforcement action that are not disclosed to any member of the public constitute investigatory records that are subject to the rules for disclosure established in § 4.64. For example, an establishment inspection report is an investigatory record and thus subject to § 4.64 except insofar as the Commissioner exercises his discretion to release it pursuant to § 4.82.

§ 4.102 Court enforcement records.

(a) All records and documents filed in the courts are available for public disclosure unless the court orders otherwise. The Food and Drug Administration will make available for public disclosure such records or documents if the agency can determine that it has an accurate copy of the actual record or document filed in the court. If the Food and Drug Administration cannot determine whether it has

an accurate copy of such a record or document, the person requesting a copy shall be referred to the court involved.

(b) After a recommendation for court action has been finally refused by a United States attorney, the correspondence with the United States attorney and the Department of Justice with respect to that recommendation, including the pleadings recommended for filing with the court, is available for public disclosure. Prior to disclosure of any record specifically reflecting consideration of possible criminal prosecution of any individual, all names and other information that would identify an individual who was considered for criminal prosecution but who was not prosecuted shall be deleted unless the Commissioner concludes that there is a compelling public interest in the disclosure of such names.

§ 4.103 Correspondence.

(a) All correspondence to and from members of the public, members of Congress, organization or company officials, or other persons, except members of the Executive Branch of the Federal Government and special government employees, is available for public disclosure.

(b) Any such correspondence is available for public disclosure at the time that it is sent or received by the Food and Drug Administration unless a different time for such disclosure is specified in other rules established or cross-referenced in this part, e.g., correspondence relating to an IND notice or an NDA in § 314.14(e)(7) of this chapter.

§ 4.104 Summaries of oral discussions.

(a) All written summaries of oral discussions, whether in person or by telephone, with members of the public, members of Congress, organization or company officials, or other persons, except members of the Executive Branch of

the Federal government or special government employees, are available for public disclosure.

(b) Any such summary is available for public disclosure at the time that it is prepared by the Food and Drug Administration unless a different time for such disclosure is specified in other rules established or cross-referenced in this part, e.g., summaries of oral discussions relating to a food additive petition in § 121.51(h)(3) of this chapter.

(c) If more than one summary of an oral discussion exists in a Food and Drug Administration file, all such summaries shall be disclosed in response to any request for such summary.

§ 4.105 Testing and research conducted by or with funds provided by the Food and Drug Administration.

(a) Any list that may be prepared by the Food and Drug Administration of testing and research being conducted by or with funds provided by the Food and Drug Administration is available for public disclosure.

(b) Any contract relating to agency testing and research, and any progress report relating thereto, is available for public disclosure.

(c) The results of all testing or research conducted by or with funds provided by the Food and Drug Administration, such as toxicological testing, compliance essays, methodology studies, and product testing, are available for public disclosure when the final report is complete and accepted by the responsible Food and Drug Administration official, after deletion of any information that would reveal confidential investigative techniques and procedures, e.g., the use of "markers" to document adulteration of a product. If such results are disclosed in an authorized manner to any member of the public before the final report is available, they are immediately available for public disclosure to any member of the public who requests them.

(d) Access to all raw data, slides, worksheets, and other similar working materials shall be provided at the same time that the final report is disclosed.

§ 4.106 Studies and reports prepared by or with funds provided by the Food and Drug Administration.

(a) The following types of reports and studies prepared by or with funds provided by the Food and Drug Administration are available for public disclosure upon their acceptance by the responsible agency official:

(1) Quarterly and annual reports of the agency.

(2) External investigations or review of agency needs and performance.

(3) Surveys, compilations, and summaries of data and information.

(4) Consumer surveys.

(5) Compliance surveys.

(6) Compliance programs, except that names of specific firms, the location of specific activities, and details about sampling numbers or sizes shall be deleted until implementation of the program is completed.

(7) Work plans prepared by Food and Drug Administration bureau, field offices, and other components, except that names of specific firms, the location of specific activities, and details about sampling numbers or sizes shall be deleted until implementation of the plan is completed.

(b) The following types of reports and studies prepared by or with funds provided by the Food and Drug Administration are not available for public disclosure:

(1) Internal audits of agency needs and performance.

(2) Records relating to the internal planning and budget process.

(3) Legislative proposals or comments prior to submission to Congress.

§ 4.107 Food and Drug Administration manuals.

(a) All Food and Drug Administration staff manuals and instructions to staff that affect a member of the public are available for public disclosure. All and other similar data and information after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician, hospital, or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as defined in § 4.81 of this chapter.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established in § 4.61 of this chapter.

(7) All correspondence and written summaries of oral discussions relating to the NADA, in accordance with the provisions of Part 4 of this chapter.

(f) All safety and effectiveness data and information not previously disclosed to the public are available for public disclosure at the time that any one of the following events occurs:

(1) The NADA has been abandoned and no further work is being undertaken with respect to it.

(2) A final determination is made that the NADA is not approvable, and all legal appeals have been exhausted.

(3) Approval of the NADA is withdrawn, and all legal appeals have been exhausted.

(4) A final determination has been made that the animal drug is not a new animal drug.

(5) A final determination has been made that the animal drug may be marketed without submission of such safety and/or effectiveness data and information.

(g) The following data and information in an NADA file are not available for public disclosure unless they have been previously disclosed to the public as defined in § 4.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 4.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(h) For purposes of this regulation, safety and effectiveness data include all studies and tests of an animal drug on animals and all studies and tests on the animal drug for identity, stability, purity, potency, and bioavailability.

PART 146—ANTIBIOTIC DRUGS FOR VETERINARY USE: PROCEDURAL AND INTERPRETATIVE REGULATIONS

9. In Part 146, by adding the following new section:

§ 146.16 Confidentiality of data and information in an investigational new animal drug notice and a new animal drug application file for an antibiotic drug.

(a) The rules established in §§ 135.33 and 135.33a of this chapter with regard to the confidentiality of an investigational new animal drug notice and a new animal drug application file shall apply to such notices and files for antibiotic drugs for new animal drug use.

(b) All records showing the Food and Drug Administration's testing of and action on a particular lot of a certifiable antibiotic drug for veterinary use are immediately available for public disclosure.

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

10. In Part 312, by adding new § 312.5 to read as follows:

§ 312.5 Confidentiality of data and information in an investigational new drug notice (IND).

(a) The existence of an IND notice will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an IND file shall be handled in accordance with the provisions established in § 314.14 of this chapter for the confidentiality of data and information in new drug applications.

(c) Notwithstanding the provisions of § 314.14 of this chapter, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational new drug has been used a copy of any adverse reaction relating to such use.

PART 314—NEW DRUG APPLICATIONS

11. In Part 314:

a. By revising the heading and paragraph (b) of § 314.11 to read as follows:

§ 314.11 Master files.

• • • • •

(b) Section 301(j) of the act makes it an offense to divulge to unauthorized persons any information acquired from a new-drug application concerning any method or process that is a trade secret. Basic manufacturers sometimes submit data to the Food and Drug Administration in the form of so-called master files for the purpose of establishing the safety of ingredients that may be used in new drugs and authorize specified applicants to incorporate by reference such data in support of their applications. The confidentiality of such data shall be determined in accordance with Part 4 of this chapter and § 314.14. Because the applicant is legally responsible for the composition of the new drug and all its ingredients and may require information in the master file for judicial or administrative proceedings concerning the drug, the Food and Drug Administration will not withhold such information from the applicant when his need for it arises and he submits a written request for it. The Food and Drug Administration will inform the person who submitted the data of any such requests.

b. By adding new § 314.14 to read as follows:

§ 314.14 Confidentiality of data and information in a new drug application (NDA) file.

(a) For purposes of this section the "NDA file" includes all data and information submitted with or incorporated by reference in the NDA, IND's incorporated into the NDA, supplemental NDA's; reports under §§ 310.300 and 310.310 of this chapter, master files, and other related submissions. The availability for public disclosure of any record in the NDA file shall be handled in accordance with the provisions of this section.

(b) The existence of an NDA file will not be disclosed by the Food and Drug Administration before an approvable letter has been sent to the applicant, unless it has previously been publicly disclosed or acknowledged. The Director of the Bureau of Drugs will maintain a list available for public disclosure of pending NDA's for which an approvable letter has been sent to the applicant.

(c) If the existence of an NDA file has not been publicly disclosed or acknowledged, no data or information in the NDA file are available for public disclosure.

(d) If the existence of an NDA file has been publicly disclosed or acknowledged before an approval letter has been sent to the applicant, no data or information contained in the file is available for public disclosure before such letter is sent but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange of important regulatory information with a foreign government.

(e) After an approval letter has been sent to the applicant for a pending NDA, the following data and informa-

tion in the NDA file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information previously disclosed to the public, as defined in § 4.81 of this chapter.

(2) A summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the NDA file. Such summaries do not constitute the full reports of investigations under section 505 (b)(1) of the act (21 U.S.C. 355(b)(1)) on which the safety or effectiveness of the drug may be approved. Such summaries shall consist of the following:

(i) For an NDA approved prior to July 1, 1975, internal agency records that describe such data and information, e.g., a summary of basis for approval or internal reviews of the data and information, after deletion of:

(*a*) Names and any information that would identify patients or test subjects or the investigators.

(*b*) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(ii) For an NDA approved on or after July 1, 1975, a summary of such data and information prepared in one of the following two alternative ways shall be publicly released when the approval letter is sent.

(*a*) The Bureau of Drugs may at an appropriate time prior to approval of the NDA require the applicant to prepare a summary of such data and information, which will be reviewed and, where appropriate, revised by the Bureau.

(*b*) The Bureau of Drugs may prepare its own summary of such data and information.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 4.61 of this chapter.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as defined in § 4.81 of this chapter.

(6) An essay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established in § 4.61 of this chapter.

(7) All correspondence and written summaries of oral discussions relating to the NDA file, in accordance with the provisions of Part 4 of this chapter.

(f) All safety and effectiveness data and information not previously disclosed to the public are available for public disclosure at the time that any one of the following events occurs:

(1) The NDA has been abandoned and no further work is being undertaken with respect to it.

(2) A final determination is made that the NDA is not appropriate, and all legal appeals have been exhausted.

(3) Approval of the NDA is withdrawn, and all legal appeals have been exhausted.

(4) A final determination has been made that the drug is not a new drug.

(5) A final determination has been made that the drug may be marketed without submission of such safety and/or effectiveness data and information.

(g) The following data and information in an NDA file are not available for public disclosure unless they have been been previously disclosed to the public as defined in §4.81 of this chapter or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 4.61 of this chapter:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(h) The compilations of information specified in § 4.117 of this chapter are available for public disclosure.

(i) For purposes of this regulation, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests on the drug for identity, stability, purity, potency, and bioavailability.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

12. In Part 431, by adding a new Subpart D to read as follows:

Subpart D—Confidentiality of Information

AUTHORITY: Pub. L. 90-23, 81 Stat. 54-56, as amended by 88 Stat. 1561-1585 (5 U.S.C. 552).

Subpart D—Confidentiality of Information

§ 431.70 Confidentiality of data and information in an investigational new drug notice for an antibiotic drug.

(a) The existence of an IND notice for an antibiotic drug will not be disclosed by the Food and Drug Administration unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an IND file for an antibiotic drug shall be handled in accordance with the provisions established in § 431.71.

(c) Notwithstanding the provisions of § 431.71, the Food and Drug Administration shall disclose upon request to an individual on whom an investigational antibiotic has been used a copy of any adverse reaction report relating to such use.

§ 431.71 Confidentiality of data and information in an antibiotic drug file.

(a) For purposes of this section, an "antibiotic drug file" includes all data and information submitted with or incorporated by reference in any form submitted pursuant to §§ 431.50 or 431.60, IND's incorporated into any such form, master files, and other related submissions. The availability for public disclosure of any record in the antibiotic drug file shall be handled in accordance with the provisions of this section.

(b) The existence of an antibiotic drug file will not be disclosed by the Food and Drug Administration before an approvable letter has been sent to the applicant, unless it has previously been publicly disclosed or acknowledged. The Director of the Bureau of Drugs will maintain a list

available for public disclosure of pending Forms 5 for which an approvable letter has been sent to the applicant.

(c) If the existence of an antibiotic drug file has not been publicly disclosed or acknowledged, no data or information in the antibiotic drug file is available for public disclosure.

(d) If the existence of an antibiotic drug file has been publicly disclosed or acknowledged before an approval letter has been sent to the applicant, no data or information contained in the file is available for public disclosure before such letter is sent, but the Commissioner may, in his discretion, disclose a summary of such selected portions of the safety and effectiveness data as are appropriate for public consideration of a specific pending issue, e.g., at an open session of a Food and Drug Administration advisory committee or pursuant to an exchange or important regulatory information with a foreign government.

(e) After an approval letter has been sent to the applicant for a pending antibiotic drug file, the following data and information in the NDA file are immediately available for public disclosure unless extraordinary circumstances are shown:

(1) All safety and effectiveness data and information.

(2) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 4.61 of this chapter.

(3) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information, after deletion of:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(4) A list of all active ingredients and any inactive ingredients previously disclosed to the public as defined in § 4.81 of this chapter.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 75-1608

PETER H. FORSHAM, *et al., Plaintiffs,*

v.

DAVID MATHEWS, *et al., Defendants.*

ORDER

Upon consideration of plaintiffs' motions for summary judgment and expedited relief, defendant Klimt's motion to dismiss and to quash service of process, federal defendants' motion to dismiss or in the alternative, for summary judgment, the Oppositions thereto, the memoranda of the parties in support thereof and in opposition thereto, and the entire record herein, the Court finds that (1) no official or employee of the Department of Health, Education and Welfare (HEW), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), or the National Institutes of Arthritis, Metabolism and Digestive Diseases (NIAMDD) is now or has ever been in possession of raw data in issue relating to the University Group Diabetes Program (UGDP) (*See* Affidavits of Theodore M. Cooper, M.D. and Donald Whedon, M.D., Federal Defendants' Motion to Dismiss or, in the alternative, for Summary Judgment); (2) the raw data in question in the property of the individual investigators and UGDP study coordinating enter and remains in the possession, custody and control of the UGDP study coordinating center (*See* Affidavit of Donald Whedon, M.D., *supra*); (3) neither the individual investigators nor the UGDP study coordinating center is an "agency" within the purview of the Freedom of Information

Act, 5 U.S.C. § 552[1]; and (4) consequently, the raw data in issue are not "agency records" subject to the disclosure provisions of the Freedom of Information Act, 5 U.S.C. § 552(B).

It is, accordingly, by th Court this 1st day of February, 1976,

ORDERED that plaintiffs' motion for summary judgment should be, and the same is hereby, denied. And it is further

ORDERED that defendants' motions to dismiss should be, and the same are hereby, granted.[2]

/s/ HOWARD F. CORCORAN
Howard F. Corcoran
Judge

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[1] For purposes of the FOIA, an "agency" includes "any executive department, military department, Government corporation, Government controlled corporation, or other establishment in the executive branch of the Government (including the Executive Office of the President), or any independent regulatory agency." 5 U.S.C. § 552(e).

[2] The remaining motions for expedited relief and to quash service of process are denied as moot.

UNITED STATES COURT OF APPEALS
For the District of Columbia Circuit

Washington, D.C. 20001

August 19, 1977

Leonard Schaitman, Esquire
Appellate Section
Civil Division
U.S. Department of Justice
Washington, D.C. 20530

Re: No. 76-1308—*Forsham* v. *Califano, et al.*

Dear Mr. Schaitman:

The Court has directed me to write to you to request that the Secretary of the Department of Health, Education and Welfare file in this Court an original and three certified copies of the Department's Order of July 25, 1977, suspending approval of new drug applications for Phenformin. I suggest that these materials be delivered to my office (Room 5413) to facilitate their transmittal to the Court.

It will be appreciated if the requested documents could be submitted within ten (10) days from the date of this letter.

Very truly yours,

/s/ GEORGE A. FISHER
George A. Fisher, Clerk

GAF/kae

cc: Anthony J. Roccograndi, Esquire
Mary Elizabeth Kruz, Esquire

UNITED STATES DEPARTMENT OF JUSTICE
Washington, D.C. 20530
August 29, 1977

Telephone: 202-739-3418

Mr. George A. Fisher
Clerk, United States Court of Appeals
for the District of Columbia Circuit
United States Courthouse
Room 5423
3rd & Constitution Avenue, N.W.
Washington, D.C. 20001

Re: Peter H. Forsham, et al. v. Joseph A. Califano, Jr., et al. (No. 76-1308, C.A.D.C.)

Dear Mr. Fisher:

In accordance with your request of August 19, 1977, we are hand-delivering to you four certified copies of the order of July 25, 1977 of the Department of Health, Education and Welfare, suspending approval of new drug applications for Phenformin.

A copy of this letter and of the order are being sent to other counsel in the case.

Very truly yours,

/s/ MICHAEL KIMMEL
Michael Kimmel
Attorney, Appellate Section
Civil Division

Enclosures:

cc: Anthony J. Roccograndi, Esq.
Chayet & Sonnenreich, P.C.
6 Fayette Street
Boston, Massachusetts 02116

Ms. Mary Elizabeth Kurz
Assistant Attorney General
Lobby Level
201 West Preston Street
Baltimore, Maryland 21201

APPENDIX A: APPELLANT'S MOTION FOR REHEARING OF SEPT. 13, 1977

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Civil Action No. 76-1308

PETER H. FORSHAM, *et al.*, *Appellants*

v.

JOSEPH A. CALIFANO, JR., *et al.*, *Appellees*

MOTION FOR FURTHER HEARING

Come the appellants in the above-captioned matter and state as follows:

1. At oral argument of this matter on December 2, 1976, appellees stated through their counsel that the Food and Drug Administration (FDA) was undertaking an audit of the raw data of the University Group Diabetes Program (UGDP). These data were the records sought by appellants pursuant to the Freedom of Information Act (5 U.S.C. 552). Appellees further stated that copies of all data which came into FDA's possession during the course of this audit would be provided to appellants forthwith.

2. On February 9, 1977, in response to appellants' request, the FDA again agreed to send appellants copies of all UGDP documents which had come into its possession during the UGDP audit. However, the FDA also informed appellants that most of the UGDP audit had been conducted by making abstracts of the data at the UGDP Coordinating Center rather than by annually copying the data or ordering transmission of the data to the FDA for internal audit. As a result, the FDA notified appellants that the documents are not as informative as you might like." (Appendix A).

3. On May 5, 1977, appellants renewed their request for "all documents including the raw data and any abstracts thereof that were gathered as a result of the UGDP audit." (Appendix B)

4. On May 23, 1977, appellants received copies of what purported to be *all* materials gathered by the FDA during the course of the UGDP audit. (Appendix C)

5. On information and belief, appellants state that the FDA has additional documents which have come into its possession during the UGDP audit which have not been provided to appellants. Failure to provide these documents violates the provisions of the Freedom of Information Act (5 U.S.C. 552) as well as the specific assurances made by appellees during oral argument that such data would be provided to appellants forthwith.

WHEREFORE, appellants move in accordance with Rule 29 of the Federal Rules of Appellate Procedure and Rule 6 of the U.S. Appeal D.C. Circuit Rules, as follows:

1. That a hearing be convened wherein appellees can explain why appellants have not been provided copies of all documents which came into the possession of appellees during the course of the UGDP audit.

2. For such other and further relief as this Court may deem just and proper.

Respectfully submitted,

/s/ NEIL L. CHAYET
Neil L. Chayet
/s/ HARVEY W. FREISHTAT
Harvey W. Freishtat

Sept. 13, 1977

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, et al., *Plaintiffs-Appellants,*

v.

JOSEPH A. CALIFANO, JR., Secretary of Health, Education and Welfare, et al., *Defendants-Appellees.*

APPELLEES' OPPOSITION TO APPELLANTS' MOTION FOR FURTHER HEARING

Appellants have moved for a further oral hearing in the above-captioned case, alleging that a hearing is needed so that "appellees can explain why appellants have not been provided copies of documents which came into the possession of appellees during the course of the UGDP audit" (Motion, p. 2). Appellants allege, "on information and belief," that FDA has "additional documents which have come into its possession during the UGDP audit which have not been provided to appellants" (Motion, p. 2).

Appellees oppose this motion, for the following reasons:

1. As indicated in the May 20, 1977 letter from Mr. Mark A. Elengold, Freedom of Information Officer, Bureau of Drugs, Food and Drug Administration, to counsel for appellants (Appendix C to appellants' motion), the FDA has furnished appellants' counsel with certain records, with "minor deletions." The letter explains:

> In the judgement [*sic*] of the Food and Drug Administration the information deleted does not fall within the scope of your request and, in any case, is not required to be disclosed under the Freedom of Information Act. If, however, you do desire to review the deleted material, please make an additional request.

> If the agency should then deny you this information, you would have the right to appeal such denial to the Department of Health, Education, and Welfare.

The correspondence attached to appellants' motion does not indicate that any further written request was made by appellants for production of the "minor deletions" in question, or that any other written request for records has been made since May, 1977.[1]

Appellants' appropriate remedy, if they believe that FDA is in physical possession of additional records available under the Freedom of Information Act (not already furnished them pursuant to their request), is to make an administrative request in writing, and, if dissatisfied, to pursue their normal administrative and district court remedies.

The position of the government in this case is that, to the extent FDA should obtain "agency records" in the course of its audit of UGDP, and to the extent such records are not exempted from disclosure, such records will, upon written request, be provided to appellants (and to any other member of the public) in the normal course.[2] Appel-

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[1] Our own telephone inquiries to officials of FDA have confirmed that appellants have made no further written request for records pertaining to the UGDP audit. We understand that a recent oral request for certain records was made by appellants; we assume that that request will be confirmed in writing so that it can be processed in the normal course.

Appellants' counsel apparently communicated directly with officials of the Department of Health, Education and Welfare, or FDA, without bothering to inform counsel for the government in this case until filing the instant motion.

[2] This is the gist, if not the precise language, of what undersigned counsel for the government, Michael Kimmel, recalls stating at the oral argument of last December. See our brief at p. 30 n.41; 21 C.F.R. Pt. 20; *Tuchinsky* v. *Selective Service System*, 418 F.2d 155, 158 (C.A. 7, 1969).

lants are not entitled to special privileges not afforded other members of the public. They must make a "request" for existing records, 5 U.S.C. 552(a)(3), and they must pursue the normal remedies if disputes should arise.

2. The legal issue involved in this appeal pertains to records *not* in the possession of HEW or its constituent agencies, i.e., the general and complete raw data of the UGDP. Any disputes concerning data or records which at the present time are in the possession of HEW or FDA, or which are alleged to be in the possession of HEW or FDA, are separable from the present lawsuit, and should be resolved through the regular procedures.

Accordingly, appellants' motion for a further hearing should be denied.

We are authorized to state that counsel for Dr. Christian R. Klimt, the State appellee, concurs in this opposition.

Respectfully submitted,

/s/ LEONARD SCHAITMAN
Leonard Schaitman, 202-739-3321

/s/ MICHAEL KIMMEL
Michael Kimmel, 202-739-3418
Attorneys, Appellate Section,
Civil Division,
Department of Justice,
Washington, D.C. 20530.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Civil Action No. 76-1308

PETER H. FORSHAM, ET AL., *Appellants*

v.

JOSEPH A. CALIFANO, JR., ET AL., *Appellees*

ADDITIONAL ALLEGATIONS TO APPELLANTS' MOTION FOR FURTHER HEARING OF SEPTEMBER 13, 1977

Come the appellants in the above-captioned matter and due to developments ensuing since their Motion for Further Hearing of September 13, 1977 (Appendix A attached), make the following additional allegations to that motion:

1. On October 5, 1977, an evidentiary hearing was convened under 21 U.S.C. 355(e) pursuant to the Food and Drug Administration (FDA) Notice of May 6, 1977 (42 F.R. 23170) concerning proposed withdrawal of approval of the New Drug Application (NDA's) for phenformin hydrochloride. Phenformin hydrochloride is an oral hypoglycemic agent whose actions were studied by the University Group Diabetes Program (UGDP) study.

2. The aforementioned hearing was conducted on an expedited basis under 21 U.S.C. 355(e) due to an imminent hazard suspension of the NDA's for phenformin hydrochloride by the Secretary of Health, Education, and Welfare. One of the four express bases supporting the Secretary's decision to suspend was the UGDP study. (Secretary's Order at p. 38, Appendix B)

3. The Food and Drug Administration's Bureau of Drugs introduced published reports of the UGDP study as evidence at the phenformin hydrochloride administrative hearing. A Bureau of Drugs witness described the UGDP study

data as the best evidence available related to the issues of the hearing. (See Appendix C)

4. All evidence relied upon by a participant to the hearing must be submitted prior to the hearing in accordance with 21 C.F.R. 12.85. The FDA's Bureau of Drugs failed to submit any supporting date from the UGDP study, despite the fact that it relied upon such study. However, upon further requests during the administrative hearing by the Committee for the Care of the Diabetic (CCD), of which appellants are members, counsel for the FDA's Bureau of Drugs indicated a lack of knowledge on the availability of UGDP supporting data. Administrative Law Judge Daniel J. Davidson ordered Bureau of Drugs counsel to obtain all UGDP documents and data in the possession of the FDA. (See Appendix D) In response, counsel for Bureau of Drugs submitted on October 6, 1977, several documents relating to the UGDP. These documents contain fractional portions of UGDP information, not data, gleaned from a small percentage of the patient population, the subject of a limited audit of the UGDP by FDA. The Bureau of Drugs represented that these were all the materials gathered by the FDA during the course of its UGDP audit.

5. During the phenformin hydrochloride administrative hearing, the UGDP information surrendered on October 6, 1977 was analyzed by witness Samuel Beaser, M.D. The one and only incident of a phenformin related death attributed to lactic acidosis reported by the UGDP in its published report was examined and compared to one of the documents (autopsy report) turned over by FDA, pursuant to CCD's request and Judge Davidson's order. Dr. Beaser's uncontroverted testimony demonstrated that the death was due to other disease processes and, in light of the disease process, phenformin hydrochloride therapy was contraindicated. (See Appendix E)

The inclusion of this patient in the UGDP's patient population was a violation of the rules under which the UGDP data purportedly was gathered. (See Appendix E at pp. 53-54) The improper attribution of this patient's death to phenformin hydrochloride therapy provided the one piece of information on which statistics of fatal side-effects for this drug were based. Extrapolations from this flawed data were then applied by Secretary Califano to justify suspension of phenformin hydrochloride prior to utilizing normal administrative proceedings. The importance of this error is demonstrated by the fact that FDA's own witness certified that the UGDP represented the best evidence available at the phenformin administrative hearing. (See Appendix C)

6. The complete, uncontroverted discrediting of the one piece of UGDP data available and pertinent to the phenformin administrative hearing confirms the opinion of a large body of the scientific community that the entire UGDP study is seriously flawed. The confirmation emphasizes the need for availability of all the UGDP raw data for public review and analysis. Public policy requires a lowering of the barriers the FDA has constructed to delay, if not prevent, an impartial analysis of the raw data.

7. The recent developments at the phenformin hydrochloride administrative hearings provide evidence of the following:

- The FDA's lack of good faith by (1) representing to this Court in December of 1976 that all materials gathered by the FDA during the UGDP audit would be supplied to appellants; and (2) representing to appellants in May of 1977 that all materials gathered by the FDA during the UGDP audit had been supplied to appellants;
- The FDA's clear exercise of dominion and control over all the UGDP raw data as demonstrated by its

retrieval of raw data from one central location, principally through use of computer printouts; and,

- The compelling public interest in independent scientific review of the UGDP data, especially in light of the reliance of the FDA on the UGDP for decision-making affecting millions of diabetic patients and the impeachment of the UGDP's accuracy as demonstrated by a critical examination at the administrative hearing of documents—not even the raw data—which contradicted the published reports of the UGDP summaries and conclusions. The "tip of the iceberg" has provided a concrete basis—not mere speculation—to mandate that, at a minimum, the raw data reviewed by FDA in its audit must be objectively analyzed to resolve this issue once and for all.

WHEREFORE, appellants move in accordance with Rule 27 of the Federal Rules of Appellate Procedure and Rule 6 of the U.S. Appeals, D.C. Circuit Rules as follows:

1. That a hearing be convened wherein appellees can explain why appellants have not been provided copies of all data and related documents which came into the possession of appellees during the course of the UGDP audit.

2. For such other and further relief as this Court may deem just and proper.

Respectfully submitted,

Neil L Chayet

Harvey W. Freishtat

Chayet and Sonnenreich, P.C.
600 New Hampshire Ave., N.W.
Suite 720
(202) 965-4150

October 26, 1977

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, *et al.*, *Plaintiffs-Appellants*,

v.

JOSEPH H. CALIFANO, JR., Secretary of Health, Education and Welfare, *et al.*, *Defendants-Appellees*.

and

CHRISTIAN R. KLIMT, Director of Clinical Investigation, University of Maryland School of Medicine, and Director, Coordinating Center, University Group Diabetes Program (UGDP), *Defendant-Appellee*.

FEDERAL APPELLEES' RESPONSE TO APPELLANTS' "ADDITIONAL ALLEGATIONS"

Appellants have submitted to the Court various evidentiary materials from an on-going administrative proceeding of the Food and Drug Administration under 21 U.S.C. 355(e). The purpose of that proceeding is to hear evidence and argument relevant to the withdrawal of FDA's approval of new drug applications (NDA's) for Phenformin. 42 Fed. Reg. 23170. None of the evidentiary materials submitted to this Court by appellants is in the record on appeal before this Court. F.R. App. P. 10(a).

Appellants have submitted these materials in support of their September 13, 1977 motion for a further oral hearing on their right of access to UGDP audit data in the possession of FDA. We have opposed that motion in our Opposition of September 23, 1977. As we then pointed out, the present appeal is concerned with appellants' action to compel disclosure of the general and complete raw data of the

UGDP. The appeal is not concerned with that portion of the UGDP data which FDA has since obtained in the course of its audit. Appellants' proper remedy as to the latter is to submit a written request to the FDA, in accordance with FDA regulations, 21 C.F.R. Pt. 20, if they believe that they have not already been supplied with all non-exempted records obtained by FDA in the course of its audit. 5 U.S.C. 552(a)(3).

We categorically reject appellants' unfounded allegation of "lack of good faith" by the government (p. 4 of appellants' submission). We also strongly oppose appellants' attempt to continue to argue their appeal in this case by making charges of various kinds in connection with an ongoing administrative proceeding in another case, the Phenformin proceeding. Appellants have no right to make their appeal in an Information Act case a general forum for their arguments in an FDA withdrawal of approval proceeding, or a springboard for gathering of evidence in that proceeding. See *NLRB* v. *Sears, Roebuck & Co.*, 421 U.S. 132, 143 n.10 (1975); our main brief, pp. 13-14. Cf. *Ditlow* v. *Schultz*, 170 U.S. App. D.C. 352, 357, 517 F.2d 166, 171 (1975).[1]

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[1] We make no attempt here to argue the merits or sufficiency evidence justifying any withdrawal of approval of Phenformin. That issue is simply not before this Court. It is before the FDA. If appellants believe that more than the published results of particular studies is needed in order to justify withdrawal of approval of Phenformin, they should make that argument to the FDA in the Phenformin proceeding, where it can be properly considered. 21 C.F.R. 12.89, 314.200(c)(3).

Appellants' September 13, 1977 motion for a further oral hearing should be denied, and their "additional allegations" should be stricken.

Respectfully submitted,

/s/ Leonard Schaitman
Leonard Schaitman, 202-739-3321

/s/ Michael Kimmel
Michael Kimmel, 202739-3418
Attorneys,
Civil Division, Appellate Section,
Department of Justice,
Washington, D.C. 20530.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

SEPTEMBER TERM, 1977

Civil Action 75-1608
No. 76-1308

PETER H. FORSHAM, *et al., Appellants*

v.

JOSEPH A. CALIFANO, JR., Secretary of the Department of Health, Education and Welfare, *et al.*

BEFORE: Bazelon, Chief Judge; Leventhal and MacKinnon, Circuit Judges

ORDER

Filed Nov. 16, 1977

It is ORDERED by the Court, *sua sponte,* that the parties to this appeal are directed to file supplemental memoranda, on or before December 5, 1977, addressing the following questions:

(1) What impact, if any, do the order of Secretary Califano of July 25, 1977 suspending new drug applications of Phenformin and the subsequent hearings have on the status of this case?

(2)(a) Have the raw data of the UGDP study been made available to appellants, or is it likely that these data will be made available to appellants in the forseeable future, either in connection with the pending post-suspension proceedings on Phenformin or otherwise?

(2)(b) If so, will that moot the case?

(3) Should this Court remand the case to the district court for further findings in connection with either question (1) or (2)?

For the Court:
GEORGE A. FISHER, Clerk

/s/ By: ROBERT A. BONNER
Robert A. Bonner
Chief Deputy Clerk

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, *et al., Plaintiffs-Appellants,*

v.

JOSEPH A. CALIFANO, JR., Secretary of Health, Education and Welfare, *et al., Defendants-Appellees (Federal appelles),*

and

CHRISTIAN R. KLIMT, Director of Clinical Investigation, University of Maryland School of Medicine, and Director, Coordinating Center, University Group Diabetes Program (UGDP), *Defendant-Appellee (State appellee)*

SUPPLEMENTAL MEMORANDUM OF CHRISTIAN KLIMT RESPONDING TO THE COURT'S ORDER OF NOVEMBER 16, 1977

By Order dated November 16, 1977, this Court ordered defendants to file supplemental memoranda addressing three questions. This Memorandum addresses each question seriatim.

(1) What impact, if any, do the order of Secretary Califano of July 25, 1977 suspending new drug applications of Phenformin and the subsequent hearings have on the status of this case?

Defendant-Appellee Klimt submits that Mr. Califano's suspension of new drug applications of Phenformin and the subsequent hearings have no direct impact on the status of this case for the reason that administrative proceedings are separate and distinct from proceedings under the Freedom of Information Act. *See Renegotiation Board* v. *Ban-*

nercraft Clothing Co., Inc., 415 U.S. 1 (1974). Indeed Plaintiffs-Appellants' rights under this Act are "neither increased nor decreased" by separate proceedings. *N.L.R.B.* v. *Sears, Roebuck & Co.*, 421 U.S. 132, 143, ftn. 10 (1975).

(2)(a) Have the raw data of the UGDP study been made available to appellants, or is it likely that these data will be made available to appellants in the foreseeable future, either in connection with the pending post-suspension proceedings on Phenformin or otherwise?

Defendant-Appellee Klimt states that as Director of the Coordinating Center of the UGDP and as custodian of the data in question, he has not made available to Plaintiffs-Appellants any of the data requested in this proceeding and further that the UGDP Coordinating Center does not intend to make this data available to Plaintiffs-Appellants. It is Defendant-Appellee Klimt's position that the raw data requested by Plaintiffs-Appellants is the property of the UGDP, and not of the federal government, and therefore is not subject to production upon Plaintiffs-Appellants' request, neither under the Freedom of Information Act (see Appellants' Brief, heretofore filed in this case) nor under Maryland Law (See Maryland Annotated Code, Article 76A, § 3(b)(iii); 3(c)(i) and (vii). It should be noted, however, that the FDA did undertake a limited audit of the UGDP study and did obtain certain of the raw data in question. Whether or not any or all of the data so obtained by the FDA has been turned over to Plaintiffs-Appellants is unknown to Defendant-Appellee Klimt.

Even if Plaintiffs-Appellants were to obtain some or all of the data from the FDA as a result of the Phenformin proceedings, most of the data would still be unavailable since the FDA has only gained access to a limited amount of the raw data through its audit. Furthermore, Phenformin was only one of the drugs studied by the UGDP.

Accordingly, Plaintiffs-Appellants' request for data relating to Tolbutomide, the principle drug under study by the UGDP, would remain outstanding.

(2)(b) If so, will that moot the case?

It is Defendant-Appellee Klimt's understanding that the FDA has no present intention to seek through audit any additional raw data from the UGDP. In view of this fact and since Defendant-Appellee Klimt has no present intention of releasing the raw data to Plaintiffs-Appellants, it is Defendant-Appellee Klimt's position that the present appeal will not become moot.

(3) Should this Court remand the case to the district court for further findings in connection with either questions (1) or (2)?

In view of Defendant-Appellee Klimt's response to questions 1 and 2, Defendant-Appellee Klimt submits that no useful purpose would be served by a remand.

Respectfully submitted,

/s/ Francis B. Burch
Francis B. Burch
Attorney General of Maryland

/s/ David H. Feldman
David H. Feldman
Assistant Attorney General

/s/ Mary Elizabeth Kurz
Mary Elizabeth Kurz
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Attorneys for Defendant-Appellee
Dr. Christian R. Klimt

I HEREBY CERTIFY that on this 1st day of December, 1977, copies of the aforegoing Supplemental Memorandum of Christian Klimt Responding to the Court's Order of November 16, 1977 were mailed postage prepaid, to Neil L. Chayet, Esq., Harvey W. Freishtat, Esq. and Chayet & Sonnenreich, P.C., 6 Fayette St., Boston, Massachusetts 02116, Attorneys for the Plaintiffs-Appellants and to the Honorable Griffin Bell, United States Attorney General.

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, et al., *Plaintiffs-Appellants,*

v.

JOSEPH A. CALIFANO, JR., Secretary of Health, Education and Welfare, et al.,
Defendants-Appellees (Federal appellees),

and

CHRISTIAN R. KLIMT, Director of Clinical Investigation, University of Maryland School of Medicine, and Director, Coordinating Center, University Group Diabetes Program (UGDP),
Defendant-Appellee (State appellee).

SUPPLEMENTAL MEMORANDUM OF THE FEDERAL APPELLEES RESPONDING TO THE COURT'S ORDER OF NOV. 16, 1977

By order of November 16, 1977, the Court (Chief Judge Bazelon, and Circuit Judges Leventhal and MacKinnon) directed the parties to file supplemental memoranda addressing four questions, as follows:

(1) What impact, if any, do the order of Secretary Califano of July 25, 1977 suspending new drug applications of Phenformin and the subsequent hearings have on the status of this case?

The Secretary's July 25, 1977 order suspending new drug applications for Phenformin, and the subsequent administrative hearings, have no impact on the status of this case. That is because appellants are suing in this case under the Freedom of Information Act, and their rights under

the Information Act are "neither increased nor decreased" by the pendency of related administrative proceedings. *NLRB* v. *Sears, Roebuck & Co.*, 421 U.S. 132, 143 n.10 (1975).

Nor is there any certainty (or likelihood) that appellants will obtain access to all the data they seek in this case as a result of the Phenformin proceedings.[1]

Finally, nothing in the Phenformin order or in the Phenformin proceedings has any legal or material effect on the proper resolution of the underlying issue in this case (whether the general UGDP raw data are "agency records" under the Freedom of Information Act).[2]

(2)(a) Have the raw data of the UGDP study been made available to appellants, or is it likely that these data will be made available to appellants in the foreseeable future, either in connection with the pending post-suspension proceedings on Phenformin or otherwise?

The Food and Drug Administration did obtain a small portion (quantitatively) of the UGDP data in the course of its recent audit of the UGDP; this portion (except patient-identifying information) has been made available to appellants (and to other interested persons). However, the vast bulk of the raw data of the UGDP study are still in the exclusive possession of the UGDP Coordinating Center (in the custody of State appellee Klimt). These remaining UGDP raw data are neither possessed by nor owned by any federal agency, hence are not "agency records" so far

[1] Furthermore, as pointed out in our main brief (pp. 3-4), Phenformin was only one of the drugs subject to the UGDP study. The principal drug under study was Tolbutamide.

[2] The fact that the FDA has obtained through the Secretary's auditing rights some of the UGDP data (which data have been made a part of the administrative record in the Phenformin proceeding) does not cause the remainder of the UGDP raw data (which was not obtained) to become "agency records."

as the federal appellees are concerned; and have not been made available to appellants by the UGDP Coordinating Center. Whether or not the UGDP Coordinating Center will make these data available in the foreseeable future to appellants is unknown by the federal appellees. Based on past experience it appears unlikely that the UGDP Coordinating Center will make the data available to appellants.

(2)(b) If so, will that moot the case?

Assuming that the general and complete UGDP raw data are not made available to appellants by the UGDP Coordinating Center, as appears to be the case, the present appeal will not become moot.

The FDA has no present intention of obtaining the remaining portions of the UGDP raw data through the auditing rights of the Secretary. Therefore it is unlikely that the present appeal will become moot by virtue of any possible further auditing of the UGDP raw data by FDA.

(3) Should this Court remand the case to the district court for further findings in connection with either question (1) or (2)?

If there are no genuine issues of material fact as to the correctness of the foregoing statements, no useful purpose would be served by a remand. The federal appellees believe that there are no genuine issues of material fact.

Respectfully submitted,

/s/ Leonard Schaitman
Leonard Schaitman, 202-739-3321

/s/ Michael Kimmel
Michael Kimmel, 202-739-3418
Attorneys,
Civil Division, Appellate Section,
Department of Justice,
Washington, D.C. 20530.

CERTIFICATE OF SERVICE

I hereby certify that on this 5th day of December, 1977, I served the foregoing Supplemental Memorandum for the Federal Appellees by causing copies to be mailed to:

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Harvey W. Freishtat, Esquire
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/s/ Michael Kimmel
Michael Kimmel
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UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Civil Action No. 76-1308

Peter H. Forsham, et al., *Appellants*

v.

Joseph A. Califano, Jr., et al., *Appellees*

SUPPLEMENTAL MEMORANDUM OF POINTS AND AUTHORITIES SUBMITTED PURSUANT TO THE COURT ORDER OF NOVEMBER 16, 1977

TABLE OF CONTENTS

TABLE OF AUTHORITIES

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Civil Action No. 76-1308

PETER H. FORSHAM, *et al.*, *Appellants*

v.

JOSEPH A. CALIFANO, JR., *et al.*, *Appellees*

SUPPLEMENTAL MEMORANDUM OF POINTS AND AUTHORITIES SUBMITTED PURSUANT TO THE COURT ORDER OF NOVEMBER 16, 1977

INTRODUCTION

This supplemental memorandum is filed in response to the Order of this Court of November 16, 1977. The parties in *Forsham, et al.* v. *Califano, et al.* were directed to address the following questions:

(1) What impact, if any, does the order of Secretary Califano of July 25, 1977 suspending new drug appliactions of Phenformin and the subsequent hearings have on the status of this case?

(2)(a) Have the raw data of the UGDP study been made available to appellants, or is it likely that these data will be made available to appellants in the foreseeable future, either in connection with the pending post-suspension proceedings on Phenformin or otherwise?

(2)(b) If so, will that moot the case?

(3) Should this Court remand the case to the district court for further findings in connection with either question (1) or (2)?

SUMMARY STATEMENT OF FACTS

Appellants, in this Freedom of Information Act case, (5 U.S.C. § 552), are distinguished physicians who are specialists in the treatment of diabetic patients. As individuals and as members of the Committee for the Care of the Diabetic (CCD), an unincorporated, non-profit association of physicians and diabetic patients, these appellants have been attempting to gain access to the University Group Diabetes Program (UGDP) study raw data for the purpose of objective review and analysis since 1970, when UGDP results were first published.[1] The objective of these plaintiff physicians was in 1970, and remains today, to open this unprecedented federally-funded study to review by the medical and scientific community in order to insure that government action which relies on the published summaries of the UGDP reflects credible underlying scientific data. Vitally interested in this matter is this nation's community of ten million diabetic patients.

Attempts by plaintiffs to gain access to UGDP raw data began with informal written requests in 1970. However, as the FDA, and later the Secretary of HEW, relied on the study's published results, without even examining the underlying raw data, for a series of administrative actions, appellants were drawn into these individual administrative proceedings to assert the need for an unbiased analysis of the raw data to determine if the actions based on the published results were justified. The description of the administrative actions involving the UGDP study which appellants have placed before the Court[2] reveals that the published summaries have precipitated a complete realignment through federal regulation of the treatment of diabetic patients.

[1] University Group Diabetes Program, The University Group Diabetes Program: A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients With Adult-Onset Diabetes. Part I: Design, Methods and Baseline Characteristics. Part II. Mortality Results; *Diabetes* 19 (Supp. 2): 747-830 (October 1970).

[2] Brief for the Plaintiffs-Appellants, at pp. 6-10 and Appellants Motion for Further Hearing of September 13, 1977.

Participation by appellant-physicians as individuals or as members of CCD in the challenge of Secretary Califano's imminent hazard suspension of phenformin hydrochloride (hereinafter phenformin)[3] and as participants in the FDA withdrawal hearings which ensued from that suspension, has been directed toward this goal of gaining access to the UGDP raw data and thereby placing agency action on a sound basis. Unless public access is thereby gained to all of the UGDP raw data, resolution of the present actions involving phenformin cannot be effected. Nor is the urgent need for the review of the raw data to which this Freedom of Information Act case is directed diminished since other Agency actions are proposed in reliance on the published results of the UGDP. Rather, the legal and scientific case for its production by order of this Court has been strengthened by the fact that the FDA is relying upon the UGDP in the phenformin proceedings.

RESPONSES TO COURT OF APPEALS' INQUIRIES

Set out below are specific responses to the inquiries of the Court:

> (1) *What impact, if any does the order of Secretary Califano of July 25, 1977 suspending new drug applications of Phenformin and the subsequent hearings have on the status of this case?*

The impact of the phenformin suspension and the resulting withdrawal hearing is to increase the urgency of appellants' claim. Secretary Califano relied on the UGDP study as the only controlled experiment which supported his ac-

[3] *Forsham et al.* v. *Califano*, No. 77-1408 (D.D.C., filed Sept., 1977).

tion.[4] FDA witnesses at the administrative withdrawal hearing described the UGDP study as the best evidence available on the issues before that administrative tribunal.[5] At the administrative hearing, Administrative Law Judge Daniel J. Davidson recognized the importance of the production of the underlying data, however, he felt powerless to require its production due to his lack of subpoena power.[6] He also ruled that he could not wait for the determination of this Court regarding availability of the data due to the expedited nature of the hearing following the imminent hazard suspension.[7] Administrative Law Judge Davidson reluctantly concluded that the hearing must proceed despite a failure to gain access to the raw data, concluding that the UGDP reference may have to be stricken or given no weight as evidence to support the FDA's withdrawal of phenformin.[8] Additionally, as shown in Appellant's Motion for Further Hearing, the UGDP results have been impeached based on even the available information.[9]

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[4] Order of the Secretary of Health, Education, and Welfare Suspending Approval of the New Drug Applications for Phenformin of July 25, 1977 at p. 38.

[5] Transcript of Phenformin Administrative Hearing (hereinafter Transcript) at p. 341; Phenformin Administrative Hearing Exhibit B-481, at p. 8.

[6] Transcript of Pre-hearing proceedings of October 4, 1977 at pp. 18, 19.

[7] Transcript at p. 137.

[8] Transcript at pp. 153-156.

[9] See Appendix E of Appellant's Motion for Further Hearing of September 13, 1977. As Appendix C to this memorandum of December 5th, appellants have additionally submitted for the attention of this Court the brief with accompanying appendices which CCD filed at the phenformin administrative hearing. This material is not submitted for the purposes of fact-finding by the Court, rather it is illustrative of the thorough impeachment of the UGDP study's results and the potential value of the raw data to an informed judgement on phenformin and other matters of importance to the diabetic patient.

These undisputed facts from the phenformin hearings, show the recognized importance of the UGDP underlying data on the merits of phenformin withdrawal. The actual impact of these legal proceedings is on the over 300,000 diabetic patients who, after consultation with their physicians, were receiving phenformin therapy. Their supply of phenformin was cut off on October 23, 1977. These patients continue to be irreparably harmed by decisions made which greatly affect them but are made without the benefit of public access to the raw data of the UGDP study, "the best evidence" available concerning phenformin use. For these patients, an ultimate Court reversal of the administrative withdrawal of the drug after it has been unavailable for many months or years cannot reverse the effect done to their course of therapy. A decision by this Court to require that the public have access to UGDP raw data is still in time to provide the administrative tribunal with evidence that all parties have conceded is crucial to a decision on the issues before it.

As appellees have noted in their response to Appellants' Motion for Further Hearing of September 13, 1977, the usefulness in pending litigation of information sought in a Freedom of Information action to the party seeking disclosure has not been considered a determinative factor. See *Sterling Drug* v. *F.T.C.*, 450 F.2d 698, 704-705 (D.C. Cir. 1971). And equitable principles generally have not been accepted as a rationale for *denying* requests for production under the Freedom of Information Act. *Bannercraft Clothing Company* v. *Renegotiation Board*, 466 F.2d 345, 353-354 (D.C. Cir. 1972)

However, to effectuate the Congressional policy reflected in the Act, which is to facilitate rather than limit production of information, *Department of Air Force* v. *Rose*, 405 U.S. 352, 360 (1976), courts have recognized that the public good resulting from disclosure must be weighed. "The effect on the public is the primary consideration." *G.S.A.* v.

Benson, 415 F.2d 878,880 (9th Cir. 1969). See also, *Getman* v. *N.L.R.B.*, 450 F.2d 670,678 n.25 (D.C. Cir. 1971) and *Theriault* v. *U.S.*, 503 F.2d 390, 392 (9th Cir. 1974). The beneficial effects of public access to the UGDP data will accrue to the millions of diabetic patients through a more informed decision by the District Court in *Forsham, et al.* v. *Califano*, Civil Action 77-1478, and in the decision of the Administrative Law Judge in the phenformin administrative hearing. In fact, the future course of all medical therapy for the diabetic patient would be aided, since the scope of the UGDP study is equally that broad.

2(a) *Have the raw data of the UGDP study been made available to appellants, or is it likely that these data will be made available to appellants in the foreseeable future, either in connection with the pending post-suspension proceedings on phenformin or otherwise?*

No raw data has been made available to appellants or any other members of the public. There has been no change in the government position over the last seven years, which is to shield the underlying data from critical review and, therefore, no likelihood that appellants or other members of the scientific community will gain access to the raw data unless this Court orders its production. The technical defense of the FDA evidently continues to be the location of this data outside the confines of a government office building.

On the insistence of the Administrative Law Judge, some UGDP information (*not* the raw data) of which the FDA had possession was distributed to the participants at the phenformin administrative hearing.[10] This information was

[10] The Administrative Law Judge, Daniel J. Davidson, ruled that he could not order production of the raw data due to his limited authority under FDA regulations. See Appendix A for this Order concerning production of UGDP raw data.

gathered by an FDA audit of the UGDP study data. (See Appendix B for the protocol of this audit.) It was from this second-hand collection of some of the data from a few of the patients studied which provided the materials for the testimony at the administrative hearing impeaching the UGDP study's credibility. (See Appellants' Additional Allegations to Appellants' Motion for Further Hearing of September 13, 1977.)[14]

The audit materials were the result of a limited review of UGDP raw data by personnel from the FDA's Baltimore office.[11] Selected information was taken from the raw data and recorded on special audit forms.[12] Computer retrieval was utilized.[13] During this process, the FDA was reportedly careful not to bring raw data into its office buildings and thereby compromise its legal theory. The bulk of the raw data of this federally-funded study has still not been reviewed by FDA personnel. It should be observed that the process which was employed by the auditors did not disrupt the data center in Maryland. In fact, the data is evidently stored for the purpose of easy retrieval. Further, personnel from a small district office were assigned the task rather than a deployment of large numbers of personnel.[15] Government objections to the practicality of reasonable public access to this data are thereby rebutted.

2(b) *If so, will that moot the case?*

Only the full and complete public access to UGDP raw data for the purpose of objective scientific review would moot the present action of appellants. Actions by the gov-

[11] Appendix B, at p. 1.

[12] *Id.*

[13] See Appendix B, at p. 1.

[14] See Appendix C.

[15] See Appendix A, at p. 1.

ernment over the last seven years make it clear that only through judicial order will such public access be gained. This case is not moot and there is no likelihood that it will become so in the foreseeable future.

(3) *Should this Court remand the case to the district court for further findings in connection with either question (1) or (2)?*

Further factual determinations are not required for the Court to rule on the merits of this Freedom of Information Act case. Essential facts placed before this Court relating to the phenformin proceedings are all matters of public record and not subject to dispute. Rather than indicate a need for a remand, appellants believe that these facts underline the importance of a re-evaluation of the District Court's legal conclusions by this Court.

The phenformin Administrative proceedings have answered the question which was asked on oral argument by the Court regarding the existence of adequate alternative remedies for the production of the data. Even secnd hand audit information possessed by the FDA was not given to appellants, as was promised by the attorney for federal appellees at the oral argument. Only when the Administrative Law Judge required such production was this information received by appellants. Since the oral argument before this Court, the FDA has placed primary reliance on the UGDP at the phenformin administrative hearing and for the drug's imminent hazard suspension and completed its audit of the raw data. Despite these facts that further diminish the plausibility of the FDA's major legal defense that the UGDP raw data is not an agency record, the FDA continues to withhold the data.

This intransigence violates a principle which the FDA has recognized as valid in its own regulations. If the FDA had funded the UGDP study rather than its sister HEW agency, the National Institutes of Health, 21 C.F.R. Sec.

20.109 would dictate its production. This regulation, which was issued on March 22, 1977, requires that all data obtained by FDA contract be made available for public disclosure. However, this Court need not make a ruling as broad as this FDA regulation to order public access to the UGDP underlying data. Appellants continue to assert that the following factors dictate public access to the UGDP raw data:

- it is a 100 percent federally-funded, multi-million dollar study funded by taxpayers.
- the study is the product of government coordination of 12 study centers through central planning and data storage and represents a federal government participation in research which differentiates the UGDP from the many health research and other private activities which receive federal funding.
- the scale of the UGDP study, the time required for its completion and the resources made available to it through federal funding make the study non-replicable by private efforts and a unique public resource.
- by contract and through regulation, the raw data from this study is available for government review, copying and storage in government facilities.
- the FDA has utilized its rights under contract and regulation to access to the raw data and demonstrated its complete dominion and control over this raw data through the recent audit process.
- the published reports of the UGDP study have been relied on for many administrative actions affecting a broad segment of the public.
- based on available information, the study's results have been impeached and the public's need for an unbiased review of the raw data demonstrated.

- access to the data is sought by responsible, expert professionals qualified in the area of the study who can properly utilize the opportunity of access to the raw data for the benefit of the medical community, their patients and the Federal Government.

CONCLUSION

Wherefore, appellants move for an expedited determination by this Court entering judgment for appellants and reversing the judgment of the District Court.

Respectfully submitted,

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Dated: December 5, 1977

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, et al., APPELLANTS

v.

JOSEPH A. CALIFANO, JR., Secretary of the Department of Health, Education and Welfare, et al.

Appeal from the United States District Court
for the District of Columbia

(D.C. Civil 75-1608)

Argued December 2, 1976

Decided July 11, 1978

Harvey W. Freishtat, with whom *Anthony J. Roccograndi* was on the brief, for appellants.

Michael Kimmel, Attorney, Department of Justice, with whom *Rex E. Lee*, Assistant Attorney General, *Earl J.*

Silbert, United States Attorney and *Leonard Schaitman*, Attorney, Department of Justice, were on the brief, for Federal appellees.

Mary Elizabeth Kurz, Assistant Attorney General of the State of Maryland, with whom *David H. Feldman*, Assistant Attorney General of the State of Maryland was on the brief, for appellee, Klimt.

Before: BAZELON, LEVENTHAL and MACKINNON, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* LEVENTHAL.

Concurring opinion filed by *Circuit Judge* MACKINNON.

Dissenting opinion filed by *Circuit Judge* BAZELON.

LEVENTHAL, *Circuit Judge*: In its broad aspect this appeal presents the question whether and under what conditions data compiled by a private group that is receiving money under a federal grant-in-aid program are or become "agency records" by virtue of the fact that the agency has funded the program and has the authority to demand those records.

An action was brought by specialists in the treatment of diabetes, as individuals and a committee,[1] to obtain raw research data of the University Group Diabetes Program (UGDP). The program is a privately conducted and federally funded long-term clinical study of the treatment of diabetes, that has reported certain harmful consequences attendant upon the long-term use of oral hypoglycemic agents. Plaintiffs question the validity of the study, and are concerned lest a useful therapeutic tool be unnecessarily removed from the market. They

[1] Three physicians sue in their own behalf, and in behalf of the Committee on the Care of the Diabetic, described in the complaint as an unincorporated association of 178 physicians involved in the daily treatment and management of diabetes.

seek access to the raw data in order to implement their challenge to the study's validity.

The action was brought under the Freedom of Information Act (FOIA), 5 U.S.C. § 552. That Act is addressed to each "agency" of the Federal Government as defined.[2] Broadly speaking, and subject to exceptions, it directs each agency to make available to the public certain information, and also "agency records." It establishes the District Court's "jurisdiction to enjoin the agency from withholding agency records and to order the production of any agency records improperly withheld from the complainant." 5 U.S.C. § 552(a)(4)(B).

A. BACKGROUND

1. *The UGDP Study and the Sponsoring Institute*

The UGDP is a study funded by 13 federal grants administered by the National Institute of Arthritis, Metabolism and Digestive Diseases (hereafter sometimes Institute or NIAMDD). That institute is an "agency" under the Act, being part of the National Institutes of Health, which in turn is an organization within the Public Health Service, in the Department of Health, Education and Welfare. The grants were made under the statutory grant-in-aid authority of the Public Health Service Act, 42 U.S.C. § 241(c). The grants were made to each of 12 participating university medical centers on the basis of their applications, and a grant was made

[2] 5 U.S.C. § 552(e):

> For purposes of this section, the term "agency" as defined in section 551(1) of this title includes any executive department, military department, Government corporation, Government controlled corporation, or other establishment in the executive branch of the Government (including the Executive Office of the President), or any independent regulatory agency.

to the UGDP Coordinating Center at the University of Maryland.[3]

The pertinent background facts are presented in the affidavit of Dr. G. Donald Whedon, Director of NIAMDD:

> 4. The inspiration for the UGDP study came from private non-government physicians and scientists in mid-1959. Between 1959 and 1961, before the study actually began with the entry of the first patients, the design, methods, and objectives of the study were evaluated by persons associated with the UGDP and representatives of NIAMDD. The Food and Drug Administration was not involved in the planning, in-

[3] The institutional grantees are:

Case-Western Reserve University
Cincinnati, Ohio
Greater Baltimore Medical Center
Towson, Maryland
Jewish Hospital and Medical Center of Brooklyn
Brooklyn, New York
Virginia Mason Research Center
Seattle, Washington
Massachusetts General Hospital
Boston, Massachusetts
Rush-Presbyterian-St. Luke's Medical Center
Chicago, Illinois
University of Alabama
Birmingham, Alabama
University of Cincinnati
Cincinnati, Ohio
University of Maryland
Baltimore, Maryland
University of Minnesota
Minneapolis, Minnesota
University of Puerto Rico
San Juan, Puerto Rico
Washington University of St. Louis
St. Louis, Missouri
West Virginia University
Morgantown, West Virginia

> ception, or design of the UGDP study. The study was funded by NIAMDD as part of its responsibility to support research in the field of diabetes and not with any specific regulatory objective in mind.
>
> * * * * *
>
> 9. The UGDP raw data (e.g., patient charts and forms) are the property of the individual investigators and the Coordinating Center and are not owned by NIAMDD. Furthermore, it is not the normal practice of NIH or this Institute to require grantees to submit their raw data for review and, in fact, submission of raw data to the institute is extremely rare. Management of the day-to-day operations of grant-supported activities is the responsibility of the grantee. Supervision of the grantee's funded activities by this Institute is generally limited to review of periodic reports submitted by the grantee. (45 CFR §§ 74.80, 74.82). Due to the large number of research grants outstanding—currently approximately 1800—it would not be physically possible for the Institute to subject raw data, if submitted, to critical review, and to require submission of the raw data of the UGDP study would have been an extraordinary requirement. It is the practice to evaluate applications for renewal grants on the basis of progress reports and final reports submitted to NIH. This practice was followed with respect to the UGDP grants. No specific provisions of the UGDP grants required submission of raw data to the Department of Health, Education and Welfare. Pursuant to 45 CFR § 74.23, officers or employees of the Department could obtain access to the raw data for purposes of audit inspection and copying if access is deemed pertinent to the grant. The raw data which are the subject of this case have never been seen by, or been in the possession of, any officer or employee of the National Institutes of Health. * * *

The particular documents sought by the plaintiffs in this case are observations on over 1000 diabetic patients,

who were monitored from 5 to 8 years. It is estimated that there are some 55 million such documents.

In June, 1970, the UGDP investigators made a presentation of the methods and initial results of their study at the annual meeting of the American Diabetes Association. The results indicated that the administration of tolbutamide (an oral hypoglycemic drug) to mild adult-onset diabetics led to a death rate from cardiovascular disease higher than that of groups treated with diet alone, with a fixed dosage of insulin, or with a variable dosage of insulin. The findings were published in the December 1970 Journal of the American Diabetes Association. During 1970 and 1971, over a dozen articles were published in medical journals concerning the study, some supportive and some critical.[4]

The NIAMDD contracted in 1972 with the Biometric Society, a private international professional society of biostatisticians, for an in-depth assessment of the quality of the UGDP study. The Society made a report to the Institute in 1974 that apparently found some merit on both sides of the controversy. It concluded that while some of the criticisms of the UGDP study were valid most were unpersuasive, and the evidence of harmfulness adduced in the UGDP study was "moderately strong." This was made public in the American Medical Association Journal for February 1975.[5]

2. *Food and Drug Administration*

The Food and Drug Administration of HEW, on being apprised of the UGDP results, issued in its October, 1970, Bulletin to the medical community a recommendation that tolbutamide should be used only in cases of adult-onset,

[4] For a listing see 40 Fed. Reg. at 28592.

[5] 131 AMAJ 615.

stable diabetes that could not be controlled by diet and could not be treated with insulin. A June, 1971, FDA bulletin proposed changes in labeling of oral hypoglycemic drugs to warn of cardiovascular hazards. Plaintiff committee sued to enjoin the proposed labeling on ground of deficiencies in the UGDP study, and the First Circuit remanded to the FDA for exhaustion of administrative remedies.[6]

The FDA deferred further action on the labeling pending the review of the UGDP study by the Biometric Society. As already noted, the 1974 report of the Biometric Society was mixed, but overall found "moderately strong" evidence of harmfulness in the UGDP study. Its contract with NIAMDD did not require the Society to seek access to the UGDP raw data, but it apparently did examine some of the raw data.[7] The contract did not require the Society to submit any raw data to the Institute, and none was submitted.

[6] Bradley v. Weinberger, 483 F.2d 410 (1st Cir. 1973). Plaintiffs contended *inter alia* that prior to regulatory action, the UGDP raw data should be made available to the scientific community. In reversing a preliminary injunction restraining the proposed relabeling, the First Circuit remanded to the FDA, ruling that the underlying questions required review on the full administrative record. Judge Coffin's opinion takes note (p. 414, fn.4) of plaintiffs' contention that the record must include, *inter alia*, the original patient records of the UGDP study, and continues: "While in light of our discussion we need not resolve the propriety of each of these requests, we reiterate what we recently said in an analogous situation: 'We think the law requires production of the entire administrative record . . . where the correctness of factual findings are [sic] involved. . . ."

[7] Plaintiffs say this access was impaired by Society-imposed limitations: to data for only one of the hypoglycemics studied, and only the period prior to October 1969.

3. *FOIA requests and District Court proceedings*

Stressing that the raw data had been made available to the Biometric Society, plaintiffs' committee began a series of FOIA requests in 1974 and 1975 for access to the raw data and a copy of the draft report of the Biometric Society. Plaintiffs were given preliminary galley proofs of the report later published in the AMAJ. HEW notified plaintiffs on August 7, 1975, that the raw data were the property of those engaged in the UGDP study and had not been reviewed or even seen by either the UGDP sponsor (NIAMDD) or FDA.

This FOIA action was begun on September 30, 1975. The complaint sought the production of the raw data, defined as consisting of the forms transmitted to the Coordinating Center and the computer tapes and/or programs on the basis of which the data were analyzed. The complaint also sought a draft report of the Biometric Society.[8]

On Feb. 5, 1976, the district court granted the motion of the HEW officials to dismiss the complaint, on the ground that no official or employee of HEW is now or has ever been in possession of the raw data relating to UGDP, that these raw data are the property of the individual investigators and UGDP study coordinating center, and in the Center's possession, custody and control; that neither the investigators nor the Coordinating Center is an "agency" within 5 U.S.C. § 552, and that the raw data are not "agency records" subject to the disclosure provisions of FOIA.[9]

[8] It is not clear what draft report is intended, other than the galley proofs already supplied of the subsequently published in February, 1975, see fn.5, above.

[9] The district court dismissed as moot a motion by defendant Dr. Klimt, the director of the UGDP Coordinating Center at the University of Maryland, to quash service of process. Dr. Klimt's directorship was based on his position as Director of Clinical Investigation in its School of Medicine. He was represented by the office of the Attorney General of Maryland.

4. *Developments pending appeal*

On July 25, 1977, while the appeal to this court was pending, Secretary of HEW Califano issued an imminent hazard order suspending new drug applications for phenformin (another oral hypoglycemic drug), and there ensued administrative withdrawal hearings. This court requested supplemental memoranda of the parties on the question of whether data that would become available to plaintiffs as a result of these administrative proceedings would moot the present controversy. The federal appellees put it that there is neither certainty nor likelihood that plaintiffs will obtain access to all the data they seek as a result of the phenformin proceeding. They note, for one thing, that phenformin was only one of the oral hypoglycemic drugs subject to the warning of the UGDP study, the principal one being tolbutamide.

However, it appears that the FDA did examine certain of the underlying raw data (a small portion, quantitatively) in the course of a recent limited audit of the UGDP, and that this portion of the underlying information (except patient-identifying information) has been made available to plaintiff-appellants, and to other interested persons, participating in the phenformin proceeding. The federal appellees' memorandum states: "The FDA has no present intention of obtaining the remaining portions of the UGDP raw data through the auditing rights of the Secretary."

B. ANALYSIS

We rule that the public at large does not have a right under the Freedom of Information Act to the underlying

raw data in the hands of the investigators and university groups who conducted the UGDP study program of diabetes under grants from the federal government.

1. The plaintiffs are a respected group of medical specialists asserting that their access to the data would inure to the public interest, by virtue of their concern that the use of drugs they deem valuable may be inhibited. We begin our analysis by observing that in this proceeding under the Freedom of Information Act, the court cannot give any weight to such a consideration.

The only claim ascertainable in this FOIA action is the right of any member of the public, motivated by whatever reasons. The Freedom of Information Act does not depend on a showing of need or interest by the particular applicant for the records. Any showing of need or interest is irrelevant.[10] Such considerations as need, interest, or public interest may bear on the agency's determination of the order of processing applications, but they have no bearing on the substantive right under FOIA to access to the document.[11]

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[10] Sterling Drug, Inc. v. FTC, 146 U.S.App.D.C. 237, 244, 450 F.2d 698, 705; Robles v. EPA, 484 F.2d 843, 847 (1973), repeating the quotation from K. Davis, Administrative Law, 1970 Supp. § 3A.22 (disclosure was never to "depend upon the interest or lack of interest of the party seeking disclosure").

See also K. Davis, id. at § 3A.29: "The Act never takes into account the need of the party seeking the disclosure; it never calls for balancing that need against the interest of a party adversely affected by disclosure. This policy choice reflects pressure from the press that 'the public as a whole has a right to know.'"

[11] It is not relevant under FOIA that the published results of the UGDP were controversial; or that, as plaintiffs allege, the government relied on these results. If the Government examined "UGDP raw data at first hand" (dissent at 10), such data have become agency records and are subject to FOIA. If the Government has relied on results of a study

2. To avoid any possible misunderstanding, we articulate that our ruling embodies no implication as to whether plaintiff physicians will have a right of access to the data underlying the UGDP study in connection with any existing or future actions of the Food and Drug Administration. That issue is distinctly different from what is before us now, and would have to be decided in the light of the record before the FDA.[12]

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based on data that it has not examined, a challenge that this was arbitrary—a matter we do not here decide—may proceed by well-established mechanisms independent of FOIA.

[12] Plaintiffs' memorandum puts it that the First Circuit's opinion impliedly recognizes such a right. While a glimmer of sympathy for plaintiffs' position may be extracted from a reference in that opinion, tucked away in a discreet footnote, all that is said by the court is that the case in court must be determined on the basis of the entire administrative record. The issue here is whether the data in the hands of the researchers are part of the agency's records.

The issue of fairness to plaintiffs will require attentive consideration in the light of the administrative record. When issues of risk of harm are involved, an agency may use results of scientific researchers even without access to underlying data, as is evidenced by the frequent use of foreign studies, *see e.g.*, Ethyl Corp. v. EPA, 176 U.S.App.D.C. 373, 400, 541 F.2d 1, 28 (en banc), *cert. denied*, 426 U.S. 941 (1976). In the present case the government has undertaken some audit review of the raw data. Plaintiffs' memorandum argues that this audit was subject to limitations that undercut its utility, but obviously we cannot appraise that issue on the record before us at this time. A court reviewing the situation on the entire administrative record would also take into account the appraisal of the Biometric Society. We cannot on our record appraise its work and its significance, let alone either plaintiffs' aspersions on the way in which that Society's committee conducted itself or the government comment that its membership embraced a wide span of scientific opinion.

The Biometric Society set forth flaws in the work of the UGDP investigators, but when an investigation requires a protracted period flaws are not wholly unexpected, and their

The FDA and NIAMDD are both in HEW, but that department is a conglomerate that embraces many and distinctly different activities. Insofar as it is engaged, through FDA, in a regulatory program, it may be subject to requirements of revelation that go beyond the FOIA's rules that govern all agencies. The FDA's regulatory actions are not before us in this FOIA lawsuit, which focuses on whether data become HEW records by virtue of study and granting activities (of NIAMDD).

3. This action requires that the persons invoking the FOIA show that they seek "agency records." The NIAMDD is a government agency, of course. But the persons or institutions who receive study grants from that Institute, or indeed from any branch of the federal government, do not on that account become government agencies.

To some extent, our path is lighted by *United States v. Orleans*, 425 U.S. 807 (1976). The case involved the Warren-Trumble council, a community action agency operating as a non-profit corporation under Ohio law, that was funded entirely by a federal agency, the Office of Economic Opportunity. Under the Economic Opportunity Act of 1964, the OEO furnished financial assistance to a community action agency, in turn defined as one designated by the state to plan and administer a community action program of "services and activities having a measurable and potentially major impact on causes of poverty in the community." The issue was whether or not one of the activities of the Ohio community action agency, the sponsoring of recreational out-

appearance may still leave the study with utility for appraisal of risk of harm to the public. *See* Certified Color Manufacturers Assoc. v. Mathews, 177 U.S.App.D.C. 137, 543 F.2d 284 (1976). The reviewing court would also consider the reasons, if any, given in any FDA proceeding involving oral hypoglycemic drugs for denying participants access to the raw data.

ings for children, if conducted negligently, could give rise to an action under the Federal Tort Claims Act. The Supreme Court held that it could not, since the council was not a federal agency or instrumentality, and its employees not federal employees. The Court found that a critical element in distinguishing a federal "agency" from either a contractor with the federal government or a grantee of the federal government, was the federal government's "control [of] the detailed physical performance." [13]

Ou decision today is congruent with our decision in *Washington Research Project v. HEW*, 164 U.S.App.D.C. 169, 504 F.2d 238 (1974), which reversed a district court order granting disclosure of certain reports made to the National Institute of Mental Health, a unit of the Public Health Service of HEW. The case involved reports made, on applications for research support, by peer review groups ("initial review groups" or IRG). The IRG peer review system was established by the government to assure competent evaluation of proposals through the use of "expertise of nongovernmental consultants functioning in panels organized around particular specialized disciplines within the broader field of biomedicine." [14]

[13] At fn. 5, 425 U.S. at 816, the Court put it that the issue was whether "there was day to day control of a program," it being irrelevant whether the program was funded by means of a contract or grant. The Court stressed (425 U.S. at 815): "Billions of dollars of federal money are spent each year on projects formed by people and institutions . . . responsible to the United States for compliance with the specifications of a contract or grant, but they are largely free to select the means of its implementation." The Court found it irrelevant that the local council did not obtain funds from any other sources or conduct any programs without federal money (425 U.S. at 818 n.7).

[14] 504 F.2d at 242.

The reports sought included a "site visit" to observe the pertinent experimental technique, and a "summary statement" of the observations and deliberations of the group, prepared by a NIMH staff member assigned to assist the group. The legal issue focused on whether the initial review group was itself a government "agency," in which case its own reports would be "final opinions" required to be disclosed under FOIA, and not intra-agency memoranda excluded under exemption 5. Acknowledging the "myriad organizational arrangements for getting the business of the government done," [15] the court concluded that "the IRG's are advisory committees, performing staff functions through the medium of outside consultancy, and are not agencies." [16] It observed, significantly, "Employing consultants to improve the quality of the work that is done cannot elevate the consultants to the status of the agency for which they work unless they become the functional equivalent of the agency, making its decisions for it." [17]

4. Plaintiffs seek to avoid a head-on contention that federal grantees be assimilated as federal agencies. Instead they emphasize a congeries of considerations that they think cumulate to a right of public access to documents in the hands of the grantees.

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[15] 504 F.2d at 246.

[16] 504 F.2d at 246.

[17] 504 F.2d at 248. Such consultants are employed and paid under the Public Health Service Act, 42 U.S.C. §§ 210, 217a. The court acknowledged that the consultant group's recommendations were undoubtedly "an often crucial element" in the approval process of the government, which was often typically a "perfunctory review." It regarded the degree of scrutiny as irrelevant to the court's consideration, stating that the fact that the government "may be greatly influenced by the IRG's expert view does not make the IRG an agency."

In addition to the responsibility of plaintiffs and a claim of public interest in their access, which we have already shown to be irrelevant, plaintiffs stress the following: This was a multi-million dollar study, entirely funded by the federal government, of such a scale as to be non-replicable by private efforts and a unique public resource. By contract and regulation, the raw data underlying the study are available for government review, copying and storage. The government's exercise of its rights of audit demonstrates its "complete dominion and control" over the data through the audit process.

The Institute's grant documents establish its right of access to "any books, documents, papers, and records of the grantees" for certain purposes. To the extent that the language of the grant is material, it indicates that these are not agency records prior to the exercise of that right.

Plaintiffs' claim is in effect an assertion that the federal government should be required—formally or constructively—to exercise its contract-grant right of access in order to provide general public access. We cannot accept this proposition. The Freedom of Information Act only gives a right of access to agency records in existence. It does not confer a right to have the government generate agency records, either by creation, subpoena or contract demand. That conclusion is implicit in *NLRB v. Sears, Roebuck & Co.*, 421 U.S. 132 (1975). The Court there granted the public a right to the production of the agency's appeal memorandum, pursuant to its understanding that the Act "represents a strong congressional aversion to 'secret [agency] law.'" (421 U.S. at 153). However the Court held that the public had no right to a judicial requirement that the agency produce or create explanatory material in the case of an appeals memorandum that referred only conclusorily to the "circumstances of the case." See 421 U.S. at 161:

> The Act does not compel agencies to write opinions in cases in which they would not otherwise be required to do so. It only requires disclosure of certain documents which the law requires the agency to prepare or which the agency has decided for its own reasons to create.

The governing principle is that only if a federal agency has created or obtained a record (or has a duty to obtain the record)[18] in the course of doing its work, is there an agency record that can be demanded under FOIA.[19]

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[18] Judge MacKinnon's opinion leads me to acknowledge that this parenthetical reference is, strictly speaking, dictum. Yet in rejecting the claim that there is an FOIA entitlement because of the *power* of the agency to obtain a record, it seems material to observe that I see a distinction where the agency has the *duty* to obtain the record. In that instance, I do not conceive that the official may lawfully resist the claim for the document on the ground that he has chosen to violate his official duty (to obtain it). In legal terms, the claim and lawsuit are in effect a joinder of two requests, and a joinder of an action in mandamus with one under the Freedom of Information Act.

[19] We do not suggest that mere physical possession of records by a government agency is the sole criterion for determining whether they fall within the scope of FOIA. Obviously a government agency cannot circumvent FOIA by transferring physical possession of its records to a warehouse or like bailee.

Where records are created by a private entity, we believe the applicability of FOIA will turn on whether the government is involved in the core planning or execution of the program, or whether, by contrast, the entity retains its private character in bona fide fashion during the course of the endeavor that results in the records. Even in the latter situation, however, records that are examined by the government through audit rights may become agency records under FOIA—if, for example, the records are copied by the agency or come into its possession.

5. Overarching policy considerations are stressed by physician applicants. There is a plea for liberal reading of reform legislation. We agree that this reform legislation should not be niggardly construed in contravention of legislative objective. The "basic thrust" of the Act embraces "a general philosophy of full agency disclosure" subject to specific exemptions and the objective "to pierce the veil of administrative secrecy and to open agency action to the light of public scrutiny." [20]

However, the general policy of avoiding agency secrecy does not give a charter for extending the law beyond the domain of "agency" and "agency records" that is the keystone of the Act. To stretch for data in the possession of federal grantees, cannot be justified as within the fair contemplation of Congress either at the time the law was passed or amended, or even today under a doctrine of trying to reconstruct specific legislative intent in the light of the broad purposes disclosed by Congress.[21]

It is tautology to say that requiring disclosure of grantee records will promote the disclosure policies of FOIA. But disclosure is not required by the statute unless those records are agency records. Congress struck a balance in fashioning the FOIA, which precludes the boundless pursuit of one policy goal, even a dominant policy, to the exclusion of all countervailing considerations.

If the statute is to be given the kind of interpretation sought by plaintiff physicians, the impact would be

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[20] Department of Air Force v. Rose, 425 U.S. 352, 360 (1976). Opinions of this court to the same effect include Bristol Myers Co. v. FTC, 138 U.S.App.D.C. 22, 25, 424 F.2d 935, 938 (1970); Getman v. NLRB, 146 U.S.App.D.C. 209, 211, 450 F.2d 670, 672 (1971).

[21] Montana Power Co. v. FPC, 144 U.S.App.D.C. 263, 445 F.2d 739 (1970), *cert. denied*, 400 U.S. 1013 (1971).

far-reaching. The number of documents in any one study would be stupendous—reaching millions in the single case before us. The number of federal grants and contracts is not a matter of record, but as was noted in *Orleans*, they account annually for disbursements in the billions. The awesome implications of plaintiffs' contention cannot be shrugged off because modern technology permits access to documents on tape through computer printouts, without need for physical production.

Scientists engaged in research on federal grants must accept the fact that any documents filed with the federal government, whether on the scientists' own initiative or an audit or other lawful demand, are subject to FOIA. Even in scientific terms, any such audit provides a surrogate for the kind of reliability usually accorded to scientific studies by replication of experiments when feasible. However, an undertaking to be audited by responsible personnel is not the same as an agreement to accept rummaging by the world at large.

The court will not trim FOIA by speculation as to adverse motivation or reaction of the scientists.[22] Similarly, the court cannot supply the extension of the reach of the Act sought by plaintiffs by building on a policy speculation that such an extension would not throttle scientific cooperation and research. This involves matters beyond our proper sphere of judicial notice.

What is requested in this action, in our view, is an extension of the statute on claim of public interest that

[22] In considering Exemption 4 for trade secrets or commercial information, the court found it irrelevant to inquire whether non-commercial scientists are either "a mean-spirited lot who pursue self-interest as ruthlessly as the Barbary pirates did in their own chosen field," or are governed by the loftier consideration that "secrecy is antithetical to the philosophical values of science." Washington Research Proj., Inc. v. HEW, 164 U.S.App.D.C. 169, 175, 504 F.2d 238, 244 (1974).

must be appraised by the legislature which can give the subject extended study, elicit opinions from all interested sources, and consider the pro's and con's.

6. It is fitting to close by referring to the need, in any pondering of such extension of the FOIA, for considering the impact on the philosophy and purpose of Federal grant programs.

Grant programs represent a means for the governance of our society which is rooted in a pluralistic conception of the value of drawing on both private and governmental sources. A leading student of Federal grant law puts it [23]

> The grant is assistance to an autonomous grantee. The grantee is not an arm, agent or instrumentality of the grantor. The employees of the grantee are not federal employees. The torts of the grantee are not federal torts. The property of the grantee is not federal property.

The reference to "an *autonomous* grantee" is a core concept, not an incidental observation. In a grant program the federal government gets the advantage of services rendered by someone who is doing his own thing, his own autonomous thing. It is not the same as a government operation in disguise.

Through its grants to university groups, the government obtains the efforts of creative persons who flourish in an academic atmosphere. Such arrangements provide a measure of detachment and independence from the mission of the government agency. The researchers may feel the tug of government purse strings, but they also feel answerable to the standards of their academic colleagues.

Plaintiffs cite the multi-million dollar nature of the study as a reason for access. There is at least a ques-

[23] M.S. Mason, *Current Trends in Federal Grant Law-Fiscal Year 1976*, 35 FED BAR 163, 167-68 (1976).

tion whether the federal government could have conducted directly, through its own employees and resources, a study program so long in time, so broad in space, and covering so many patients and controls. Even in a case where the grant is to conduct a study that might conceivably be conducted by federal employees, there is an advantage in terms of effective government and advancement of the public interest if the study is done by various institutions. The government goes beyond the capabilities of its own employees, adding the spirit and insights of the scientists and students who have selected a different life style, at a center of learning.

As earlier noted, we are not concerned here with the kind of case where the federal government exercises detailed control over operations. Such a condition presents different considerations, as noted in *Orleans*. Nor do we have a suggestion of subterfuge, with a federal agency seeking to conduct research outside the scrutiny of government laws, by using facilities that are independent only nominally. The case before us concerns a UGDP study conceived in 1959 by private, non-government physicians and scientists. They developed their own methodology; it was not dictated by the federal government.

Of course, in any program funded by the federal government there is an opportunity for the government to assess the results of the performance and of any studies. There may also be directions by the federal government in certain matters of public policy that are essentially peripheral to the core of the work done. There may, for example, be a requirement of avoidance of discrimination on grounds of race, religion, creed or sex. There may be achievement of other government objectives which apply across the board to all activities financed by the federal government.

The central question is whether the government is really involved in the core of the program. At least in a case such as the one before us, where there was no claim of significant government control of day-by-day operation, or detailed involvement in the planning or execution of the program, the overall concept of autonomy of grantees persists, even though there are federal objectives, right of federal audit and perhaps some overarching federal requirements.

At least a fleeting reference should be made to acknowledge that some of the federal grantees are institutions of the state governments.[24] There are thus considerations of federalism involved. These are not necessarily of constitutional dimension. However, they are not without relevance in appraising the extent to which such grantees are automatically governed by rules provided by Congress for the federal agencies, such as govern access to records and meetings, or personnel management,[25] or any other rules.

The foregoing matters indicate that a balance must be struck, one that considers the advantages of grantees that are autonomous and have value because they are not governmental, and the possibly conflicting policy that cherishes full and free public access to government agencies and shuns secrecy as invidious. Such a balancing is a task for the legislature. The extension of access sought by plaintiffs on the ground of public interest is not properly addressed to the courts.

Affirmed.

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[24] See note 9, *supra*, as to University of Maryland.

[25] National League of Cities v. Usery, 426 U.S. 833 (1976).

MACKINNON, *Circuit Judge*, concurring: I join generally in Judge Leventhal's opinion but wish to add the following observations.

5 U.S.C. § 552(a)(3) provides: "[E]ach agency, upon any request for *records* . . . shall make the records promptly available to any person." 5 U.S.C. § 552(a)(4)(B) also refers to the location of "*agency records*" as constituting one basis for conferring on the district court for that district "jurisdiction to enjoin the agency from withholding *agency records* and to order the production of any *agency records* improperly withheld from the complaint. In such a case the court . . . may examine the contents of such *agency records* in camera . . . ." (Emphasis added.) A fair conclusion from the foregoing indicates that it is not just "records" but "*agency* records" that the statute is addressing.

The court's opinion at page 16 states:

> The governing principle is that only if a federal agency has obtained a record (*or has a duty to obtain the record*) in the course of doing its work, is there an agency record that can be demanded under FOIA. [Emphasis added.]

The italicized statement is not necessary to our decision and I do not join in it. Each particular case involving a request for records not in the possession of an agency but for which, it is alleged, there is some duty to obtain the records must be decided on its particular circumstances. I would leave to a future opinion any declaration as to the extent to which FOIA should be interpreted to cover records not created by, obtained by, or otherwise in the possession of an agency. The plain implication derived from the language of the statute is that it does apply to records which belong to the agency or are in its possession—that is, records which the agency has created or obtained. That is all that is needed to decide

this case. I would not refer to records about which it might be said that an agency might have some duty to obtain until such time as we are presented with a case that raises the question directly and presents to us all the relevant facts necessary to decide the applicability of FOIA to that situation.

The dissent would go even further and substitute for the normal interpretation of the language of the statute a meaning to be derived from an extraneous examination of "*all* the relevant circumstances surrounding the creation, preservation, and use of [the] particular records" (Dissent at 6, emphasis original). Then, "[i]f this analysis reveals a significant degree of federal involvement with the records, then they should be considered agency 'records' subject to FOIA" (*Id.*, footnote omitted). The *catch* is allowing the interpretation of the statute to turn upon what a judge might consider a "*significant* degree of federal involvement." The attempt is to impose a "chancellor's foot" standard which varies with each judge. The statute, however, is not susceptible of such construction, and happily so, for those whose foot gives them a short standard would find records to be "*agency* records" wherever there was any federal funding or access to the records. That standard, as applied by some courts, would extend FOIA to practically unlimited lengths in those universities and industries which engage in private research. If Congress desires the Act to be so extended, it can do so by enacting appropriate legislation; but my view coincides with that expressed in Judge Leventhal's opinion, that such an extreme extension of the Act should not be created by judicial fiat.

In reaching this conclusion, I see no harm to the public. Where particular records are the subject of legitimate inquiry, as in the two cases referred to in the dissent, they may be subpoenaed by interested parties.

BAZELON, *Circuit Judge, dissenting*: Plaintiffs seek disclosure of the raw data of a federally-sponsored research project, the University Group Diabetes Program (UGDP). The UGDP data are locked in a bank vault in Maryland in the custody of the UGDP program coordinator. For the majority, this means they are not agency "records" subject to disclosure under the Freedom of Information Act (FOIA). With all due respect, I cannot agree.

In my view, factors other than possession are relevant in determining whether the UGDP data are agency "records." The Federal Government has provided all of the funding for the UGDP; the Government has an unrestricted right of access to the data; and importantly, the Government has extensively relied on the UGDP study and data in regulatory action affecting the treatment of diabetes. I think these factors cumulatively establish a significant degree of federal involvement with the UGDP raw data. Accordingly, I would hold that they are agency "records."

I.

The Freedom of Information Act requires federal agencies to disclose all "records," 5 U.S.C. § 552(a)(3),[1] that

[1] [E]ach agency, upon request for records which (A) reasonably describes such records and (B) is made in accordance with published rules stating the time, place, fees (if any), and procedures to be followed, shall make the records promptly available to any person.

5 U.S.C. § 552(a)(3) (1974). As originally enacted, this section provided:

> [E]ach agency, on request for identifiable records made in accordance with published rules stating the time, place, fees to the extent authorized by statute, and procedure to be followed, shall make the records promptly available to any person.

[Continued]

do not fall within one of nine exemptions. *Id.* § 552(b)(1)-(9). No definition of the term "records" is found in either the Act or the legislative history.[2] The case law, focusing almost exclusively on the exemptions, sheds little light on this term.[3] We are thus left with little

[1] [Continued]

The section was amended in 1974 to make clear that "[a] 'description' of a requested document would be sufficient if it enabled a professional employee of the agency who was familiar with the subject area of the request to locate the record with a reasonable amount of effort." H.R. REP. No. 876, 93d Cong., 2d Sess. 5-6 (1974).

[2] The 1967 Attorney General's Memorandum does contain one sentence relevant to the definition of agency records. It says: "Subsection (c) [552(a)(3)] refers, of course, only to records in being and in the possession *or control* of an agency." R. Clark, Attorney General's Memorandum on the Public Information Section of the Administrative Procedure Act (1967) *reprinted in* Freedom of Information Act Source Book, S. REP. No. 82, 93d Cong., 2d Sess. 222 (1974) (emphasis added). Although the Attorney General's Memorandum is a doubtful guide to congressional intent, see K. DAVIS, ADMINISTRATIVE LAW TREATISE 117 (1970 Supp.), the fact that it refers to two criteria for defining agency "records"—possession or control—suggests a more inclusive approach than that adopted by the majority. I would also argue that the Attorney General's Memorandum is consistent with the result I would reach here, since in my view the Government involvement with the UGDP data amounts to "control."

[3] *But see* Goland & Skidmore v. CIA, No. 76-1800 (D.C. Cir., May 23, 1978) (congressional hearing transcript in possession of agency not an agency record); SDC Development Corp. v. Mathews, 542 F.2d 1116 (9th Cir. 1976) (materials in medical reference library not agency records); Cook v. Willingham, 400 F.2d 885 (10th Cir. 1968) (per curiam) (presentence report in the hands of prison authority not an agency record); Ciba-Geigy Corp. v. Mathews, 428 F. Supp. 523 (S.D. N.Y. 1977) (UGDP raw data not agency records); Nichols v. United States, 325 F. Supp. 130 (D. Kan. 1971), *aff'd*, 460 F.2d 671 (10th Cir.), *cert. denied*, 409 U.S. 966 (1972) (physical evidence relating to assassination of President Ken-

direct guidance in attempting to elucidate a key provision of the Act.

The majority does not discuss the difficulties involved in defining agency "records." It simply asserts, with little supporting rationale, that the crucial question is whether the documents have been "created" or "obtained" by a federal agency.[4] In adopting this approach, the majority joins with the federal defendants and the district court in looking to such factors as property rights and possession in defining agency "records." [5] I have no

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nedy not "records"). I exclude cases that turn on the definition of a federal "agency." *E.g.*, Soucie v. David, 448 F.2d 1067 (D.C. Cir. 1971).

[4] Maj. op. at 16. Apparently, the majority would also recognize agency "records" where the Government is involved in the "core planning or execution" of a program, maj. op. at 16 n. 19, 21; and where a federal agency has a duty to obtain records. Maj. op. at 16. *But see* concurring op. at 1.

[5] The district court found that

> (1) no official or employee of the Department of Health, Education and Welfare (HEW), the National Institute of Health (NIH), the Food and Drug Administration (FDA), or the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) is now or has ever been in possession of raw data in issue relating to the University Group Diabetes Program (UGDP) . . .; (2) the raw data in question is [sic] the property of the individual investigators and UGDP coordinating center and remains in the possession, custody and control of the UGDP study coordinating center. . .; (3) neither the individual investigators nor the UGDP study coordinator is an 'agency' within the purview of the Freedom of Information Act, 5 U.S.C. § 552; and (4) consequently, the raw data in issue are not 'agency records' subject to the disclosure provisions of the Freedom of Information Act, 5 U.S.C. § 552(B).

Joint Appendix (J.A.) at 146-47 (footnote omitted).

[Continued]

objection to title or custody as relevant criteria. I do object, however, to a test based on only some of many possibly relevant factors, with little justification offered for the primacy of these factors. The place to start in determining the scope of agency "records" is not with assertion, but with an examination of the policies of the FOIA.

There can be no doubt about the basic goals of the Freedom of Information Act. As the Senate Report put it, the fundamental premise of the Act is that "the public as a whole has a right to know what its Government is doing." S. REP.NO. 813, 89th Cong., 1st Sess. 5 (1965). FOIA was designed, in the words of the Report, "to establish a general policy of full agency disclosure unless information is exempted under clearly delineated statutory language. . . ." *Id.* at 3. In the House, Congressman after Congressman rose to speak in suport of the policy underlying the bill. This was, as they variously put it, the right to the public "to information relating to the actions and policies of Federal agencies," 112 CONG.REC. 13655 (1966) (remarks of Rep. Hall); "to know the facts about the operation of their government," *id.* at 13657 (remarks of Rep. Reid); "to be fully informed about the policies and activities of the Federal Government," *id.* at 13648 (remarks of Rep. Faschell). These statements suggest the need for a broad definition of agency "records": broad enough to let the public know everything "its Government is doing;" to illuminate all "policies and activities of the Federal Government."

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[5] [Continued]

The federal defendants' position is that "the term 'agency records' in the Freedom of Information Act applies to 'records' in the possession of a federal agency or owned by an agency, or produced under the day-to-day supervision of an agency." Gov. Br. at 17.

The principle that "the disclosure requirement be construed broadly. . . ," *Soucie v. David*, 448 F.2d 1067, 1080 (D.C.Cir. 1971), is also rooted in the structure of FOIA. Before FOIA was enacted, the public information section of the Administrative Procedure Act allowed agencies to withhold information "in the public interest," or "for good cause shown," or if the person seeking the information was not "properly and directly concerned." 5 U.S.C. § 1002 (1964). These broad exemptions created what was in effect a "withholding statute," not a "disclosure statute." [6] To remedy this situation, Congress enacted a statute containing a general disclosure section and nine narrowly drawn exemptions. The disclosure section provided that "any person" could have access to any agency "record," without having to state a reason for wanting the information. And the exemptions were drafted to provide "definitive guidelines" [7] as to what information could be withheld. To avoid new loopholes, Congress expressly limited the grounds for nondisclosure to those specified in the exemptions.[8] The objective was to "make it clear beyond doubt

[6] S. REP. No. 813, *supra* at 5.

[7] *Id.* at 3.

[8] This section does not authorize withholding of information or limit the availability of records to the public, except as specifically stated in this section.

5 U.S.C. § 552(c) (1970).

I agree that in enacting FOIA Congress struck a deliberate balance between a policy of full disclosure and various countervailing policies. Maj. op. at 17. But the legislative history makes it abundantly clear that all of the competing policies *Congress* saw fit to recognize were to be accommodated through nine specific exemptions. It comes as a surprise, therefore, to learn that a policy not mentioned by Congress—that of preserving grantee "autonomy," maj. op. at 19 is to be realized through a restrictive definition of agency "records."

that all *materials of the Government* are to be made available to the public by publication or otherwise unless explicitly allowed to be kept secret by one of the exemptions in [§ 552(b)]." S.REP.No. 813, *supra* at 10 (emphasis added in part).

Both the purpose and the structure of FOIA point to a broadly inclusive definition of agency "records"—a definition encompassing "all materials of the Government." I seriously doubt that common law notions of property or custody can define the totality of such records. In my view, the appropriate approach under the statute is to examine *all* the relevant circumstances surrounding the creation, preservation, and use of particular records. If this analysis reveals a significant degree of federal involvement with the records,[9] then they should be considered agency "records" subject to FOIA.

II.

Plaintiffs emphasize three forms of federal involvement with the UGDP research data: federal funding of the data, federal access to the data, and federal reliance on the data in administrative decisionmaking. We need not decide whether one of these factors, or even two of these factors in combination, would be sufficient to make the

[9] Another court that has grappled with whether the UGDP raw data are agency "records" concluded "that the goals and purposes of the Act would be served best by imposing a standard which calls for proof that the records were either Government-owned or subject to substantial Government control or use. In other words, it must appear that there was significant Government involvement with the records themselves in order to deem them agency records." Ciba-Geigy Corp. v. Mathews, 428 F. Supp. 523, 529 (S.D. N.Y. 1977). Although I disagree with Judge Tenney's application of this standard, particularly his conclusion that the Government has not directly relied on the UGDP raw data, *id.* at 531, I have no quarrel with his statement of the standard itself.

UGDP data agency "records." Where all three factors are present, however, I think these materials are clearly agency "records."

A. *Government Funding*

One hundred percent of the UGDP funding was provided by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), one of the institutes of the National Institutes of Health. Federal funding is significant for FOIA purposes for two reasons. First, funding of scientific research is a federal activity, and FOIA was enacted to allow the public to obtain information about all federal activities—including the expenditure of money. As one Congressman put it, FOIA was intended in part to enhance the rights and responsibilities of the voting public by making it possible for them to know "what their Government is doing with their money." 112 CONG.REC. 13659 (1966) (remarks of Rep. Gurney); *accord* 110 CONG.REC. 17088 (1964) (remarks of Sen. Dirksen).

Federal funding of the UGDP is also important because funding brings with it significant Government control over the use, maintenance, and disposition of the UGDP raw data. This can be seen by examining HEW regulations governing the relationship between the Government and the grant recipient. Under these regulations, the grantee is obliged to retain "financial records, supporting documents, statistical records, and all other records pertinent to an HEW grant" for a period of three years after receiving the grant. 42 C.F.R. § 74.20. If the granting agency determines that any of the records generated by the grantee have "long term retention value," the agency may order the records transferred to the Government for permanent custody. *Id.* § 74.20(b). At all times, the Government has the right of access to "any books, documents, papers, and records of the grantee"

for the purpose of making "audit, examination, excerpts and transcripts." *Id.* § 74.23(a). The regulations further require that the grantee retain all "[l]aboratory notes, related technical data and information" that pertain to a patentable invention, and make them available to HEW upon request. *Id.* § 52.22. And if the grantee copyrights a publication resulting from the grant, the regulations give the Government a royalty free, nonexclusive license "to reproduce, translate, publish, use, disseminate, and dispose of such materials and to authorize others to do so." *Id.* § 52.23. While these provisions probably fall short of establishing full federal ownership of the UGDP data, *see* Gov. Br. at 26-31, they do establish, I think, that the Government has a substantial degree of control over the use and disposition of the UGDP records.

B. *Government Access*

Under the HEW grant regulations, the Government has an apparently unlimited right of access to the UGDP raw data. 45 C.F.R. § 74.23(a) provides:

> HEW and the Comptroller General of the United States, or any of their duly authorized representatives, shall have access to any books, documents, papers, and records of the grantee which any of them determine are pertinent to a specific HEW grant, for the purpose of making audit, examination, excerpts and transcripts.[10]

[10] The Government may have access to the UGDP raw data under FDA regulations as well. 21 C.F.R. § 312.1(a)(12)(6)(e) gives the FDA the right of access to investigator's records relating to investigational new drugs (INDs). The UGDP holds two INDs from the FDA. J.A. at 92. The federal defendants note that the regulation requires investigators to *retain* such records for only two years after administration of an IND has been discontinued, and assert that the UGDP discontinued use of its INDs more than two years ago. Gov. Br. at 34-35. However, there is no indication that

HEW is permitted to "examine" and "excerpt" not only the financial records of the UGDP, but also raw research records. This is demonstrated by the fact that when the FDA conducted a scientific audit of the UGDP, portions of the raw data were examined by government investigators, copied, and then retained by the agency. Gov. Supp. Memo. of Dec. 5, 1977.

The Government's right of access to the UGDP raw data is important for FOIA purposes since it establishes the basis for Government compliance with FOIA requests. Obviously, the Government must be able to obtain copies of requested agency "records" quickly and without legal impediment.[11] For example, if the Government had to purchase certain data, or subpoena certain records to comply with a FOIA request, these materials might not be considered agency "records." We need not decide this question, for no such barrier is involved here. The Government can exercise its right of access to the UGDP data at any time and for any reason. To be sure, greater inconvenience may be involved in obtaining copies of documents not in the immediate custody of the agency. But, as the Government concedes, agency "records" need not be located within the physical confines of the agency.

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the UGDP has in fact discarded the records, or that the FDA *right of access* is extinguished two years after administration of an IND stops.

[11] The Act requires agencies to determine whether to comply with a FOIA request "within ten days (excepting Saturdays, Sundays, and legal public holidays) after the receipt of any such request. . . ." 5 U.S.C. § 552(a)(6)(A) (1974). An additional 10 days is permitted in "unusual circumstances," including "(i) the need to search for and collect the requested records from field facilities or *other establishments* that are separate from the office processing the request; . . ." *Id.* § 552(a)(6)(B)(i) (emphasis added). The last provision appears to specifically contemplate that agency "records" can be found outside the custody of the agency.

Gov. Br. at 20 n.32. Records may be bailed to a privately-owned warehouse, loaned to a private entity, or may have been sold or donated to the Government but not delivered. In terms of ease of compliance with FOIA, these types of situations are indistinguishable from the present case.[12]

C. *Government Reliance*

Probably the strongest link between the UGDP data and the Federal Government is found in the extensive history of federal reliance on the UGDP study and data in regulatory action dealing with the treatment of diabetes. This reliance must be viewed against the background of intense controversy surrounding the UGDP ever since the study's first conclusions were published in 1970.[13]

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[12] The majority's assertion that NLRB v. Sears, Roebuck & Co., 421 U.S. 132, 161-62 (1975) and Renegotiation Board v. Grumman Aircraft Engineering Corp., 421 U.S. 168, 192 (1975) require more than a mere right of access to documents is without foundation. These cases stand only for the proposition that FOIA does not oblige an agency to *write* opinions. They say nothing about the duty to retrieve records that are reasonably described, admittedly exist, and are within an agency's power to obtain.

[13] Klimt, Knatterud, Meinert & Prout, *The University Group Diabetes Program: A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes*, 19 DIABETES (Supp. 2) 747 (1970). Subsequent reports were published in Knatterud, Meinert, Klimt, Osborne & Martin, *Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes: IV. A Preliminary Report on Phenformin Results*, 217 JAMA 777 (1971); Goldner, Knatterud & Prout, *Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes: III. Clinical Implications of UGDP Results*, 218 JAMA 1400 (1971); Knatterud, Klimt, Osborne, Meinert, Martin & Hawkins, *A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes: V. Evaluation of Phenformin Therapy*, 24 DIABETES (Supp. 1) 65 (1975).

Release of the UGDP's initial findings, suggesting a possible correlation between oral hypoglycemic drugs and cardiovascular mortality, had a profound impact.[14] Professional conferences were convened, articles were published, and scientific studies were undertaken with the hope of evaluating the UGDP conclusions and determining their validity. The medical and scientific communities eventually divided along pro- and anti-UGDP lines. Supporters of the UGDP cited the study's cost, duration, broad patient base, and sophisticated design as confirming the validity of the findings.[15] Critics of the UGDP, on the other hand, pointed to alleged inadequacies in study design, methodology, and execution.[16] The controversy was compounded when a UGDP investigator, Dr. Angela Bowen, resigned from the study, challenging the integrity of the program director and suggesting a possible manipulation of the data base to reach results unfavorable to one of the drugs under study.[17]

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[14] Some of the controversy surrounding the UGDP study is reviewed in the majority opinion at 3-7.

[15] *See, e.g.*, Cornfield, *The University Group Diabetes Program: A Further Statistical Analysis of the Mortality Findings*, 217 JAMA 1676 (1971); Prout, Knatterud, Meinert & Klimt, *The UGDP Controversy: Clinical Trials Versus Clinical Impressions*, 21 DIABETES 1035 (1972).

[16] *See, e.g.*, Feinstein, *Clinical Biostatistics: An Analytical Appraisal of the University Group Diabetes Program (UGDP) Study*, 12 CLIN. PHARMACOLOGY, THERAPEUTICS 167 (1971). Schor, *The University Group Diabetes Program: A Statistician Looks at the Mortality Results*, 217 JAMA 1671 (1971).

[17] Dr. Bowen testified as follows before FDA at the public hearings on the proposed labeling change for oral hypoglycemic drugs:

> An even more troublesome aspect has not been as well explored. This involves the matter of personal integrity and scientific honesty of one key member of the group. This question was actively considered both privately and openly among the investigators as early as 1968. It has also been asked publicly since that time. The question that the FDA must now ask and hopefully answer is "were the data that were gathered in the field accurately and honestly recorded and reported from the coordinating center in Baltimore?" I fully recognize that this is a serious allegation but there is basis for reasonable doubt. You will recall that this was a double blind study. Investigators did not know what medication a patient was taking. Data were simply recorded and sent along to the biostatistician at the coordinating center. We then received a printout of the cumulative results. Therefore if one was told that a given death or other side effect occurred in a tolbutamide patient it was taken on faith because the investigator never knew for sure. [Tolbutamide is an oral hypoglycemic drug and a competitor of phenformin.] It did not occur to me to question this state of affairs until 1968 when the first allegation was made that the death rate was higher in the tolbutamide group. At the same meeting another investigator revealed that the biostatistician, Dr. Klimt, was a paid consultant to U.S. Vitamin, the then makers of phenformin. This was at first denied, then acknowledged. A spirited discussion followed during which the potential for abuse under such circumstances was discussed at length. This ended with the demand from the New York delegation that an independent review of the data be undertaken by outside statisticians. Dr. Klimt threatened to resign if this was done. This threat did not meet with universal disapproval, but a compromise was finally reached in which a review would be done but Dr. Klimt would be permitted to choose the reviewers! Drs. Cornfield and Brown were his choices. It is my understanding that they simply reviewed the numbers and methods sent to them by the coordinating center and that raw data were not used even then. This episode caused a rift of major proportions among the investigators.
>
> J.A. at 130-31.

Despite all the uncertainty about the validity of the UGDP study, and the inability of sceptical scientists and physicians to examine the raw data, the Federal Government has twice relied on the UGDP findings in regulatory action affecting a large segment of the public. In

1975, the Commissioner of the Food and Drug Administration (FDA) proposed new labeling requirements for oral hypoglycemic drugs used in the treatment of diabetes. 40 FED.REG. 28587 (1975). The *Federal Register* notice of the proposed warning stated in part:

> The judgment of the Commissioner that changes must be made in the labeling of the oral hypoglycemic drugs to reflect the findings of the UGDP study is well known. . . .
>
> The warning proposed in this labeling is based primarily on a thorough review and evaluation of the UGDP study. . . .
>
> The Commissioner reaffirms his view that the UGDP study is an adequate and well-controlled clinical trial, which is the most extensive and detailed examination of the long-term administration of hypoglycemic agents yet undertaken.
>
> . . . The Commissioner believes that the UGDP study is a validly conducted trial and accepts the opinion of the Biometric Society committee and other experts that the increased cardiovascular mortality found in this trial cannot reasonably be attributed to scientific shortcomings in the study.

Id. at 28591.[18] A clearer affirmation and reliance on the UGDP study is hard to imagine.

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[18] The Commissioner of FDA recognized that "[f]rom the time the results of the UGDP study were first reported, the study was subjected to intense criticism by both clinicians and statisticians." 40 FED. REG. 28588. He conceded that "a wide-spread belief had developed among many physicians that the UGDP study was somehow flawed in terms of its design and execution, and therefore could not serve as a proper basis for a warning to the medical profession." *Id.*

> The agency therefore decided to postpone implementation of the warning until [review of the UGDP study by a committee of the Biometrics Society] was published. Since the UGDP study was the basis for the proposed warning, the Commissioner believed that this independent review of the statistical validity of the study should be available to all interested persons before taking definitive action. The review by the committee of the Biometrics Society required extensive reanalysis of the data in the UGDP study and was not published until February 10, 1975.

Id. at 28589.

The Biometrics Society audit reconfirmed the Commissioner's belief in the need for regulatory action based on the UGDP.

> Although the [UGDP] has shortcomings, which might be expected in any clinical trial of this complexity, the shortcomings do not invalidate the central finding that there appears to be an increased risk of cardiovascular mortality associated with the administration of tolbutamide and of phenformin to maturity-onset diabetic patients, compared to treatment with diet alone or diet plus insulin. This conclusion has in the past been reached independently by the UGDP investigators, the FDA, and the Biometrics Society committee, and is again affirmed by the Commissioner. Other clinical trials of these oral hypoglycemic drugs are not comparable to the UGDP study and provide insufficient evidence to negate the findings of the UGDP study.

Id. at 28591.

Later, in 1977, Secretary Califano of HEW declared phenformin, an oral hypoglycemic drug, an "imminent hazard to public health" under § 505(e) of the Food and Drug Act, 21 U.S.C. § 355(e), and suspended approval of all new drug applications for this drug. The Secretary indicated that he was relying to a considerable extent on the statistical evidence gathered by the UGDP. The order stated that "[t]he FDA, which is experienced in interpreting and aanlyzing incidence figures for adverse reactions, has examined [the UGDP] statistics and concluded that the incidence figures are scientifically valid."

Order of the Secretary Suspending Approval at 11 (July 25, 1977).[19]

Significantly, the proposed labeling change and suspension of phenformin were not undertaken solely on the basis of the published studies of the UGDP. In addition, the Federal Government has twice exercised its right of access to the UGDP raw data to verify the validity of the UGDP findings. When the initial controversy over the UGDP erupted, NIAMDD retained an independent group of biostatisticians, the Biometric Society, to review the UGDP. The Society was given access to the UGDP raw data for this purpose. After conducting a partial audit, it published a report indicating support for the UGDP findings.[20] Several years later, prior to the suspension of new drug applications for phenformin, the FDA conducted its own audit of the UGDP. Details of this audit are sketchy, but the federal defendants admit that the FDA examined and copied at least a sample of the UGDP data in the course of its examination of the study. Gov. Supp. Mem. of Dec. 5, 1977 at 2.

These Government-sponsored or conducted audits are of considerable importance. By examining the UGDP raw data at first hand, the Government has apparently satisfied itself that the UGDP results are sound. In other words, the Government has relied *directly* on the UGDP raw data in the course of formulating official Government policy. As such, these data are precisely the sort of documents Congress intended to be disclosed under FOIA. *SDC Development Corp. v. Mathews*, *supra* n.3, at 1119-20.[21]

[19] The quoted passage refers to statistics from "all available sources," Order at 11, but it is clear from the context that the UGDP is included. The UGDP is also referred to at pp. 8, 38, 40-41, 46, 63 and 66.

[20] Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, *Report of the Committee for the Assessment of Hypoglycemic Agents*, 231 JAMA 583 (1975).

III.

The majority cryptically asserts that a finding that the UGDP raw data are agency "records" would interfere with the "autonomy" of federal grant recipients. The exact meaning of this is unclear. I do not maintain, nor do plaintiffs argue,[22] that the UGDP is a federal "agency." Consequently, no suggestion has been made that all of the various duties and responsibilities of a federal agency should be imposed on the UGDP. The only question before us is whether the UGDP raw data are agency "records" of HEW. An affirmative answer to this question would require *HEW*—not the UGDP—to obtain copies of these records in response to plaintiffs' FOIA request. No direct interference with the manner or method in which a grantee conducts its research would result.

Perhaps the majority's reference to "autonomy" means to suggest that scientific activity would be chilled by the knowledge that data produced under a federal grant

[21] In emphasizing the Government's reliance on the UGDP study and data, I do not imply that the court should give weight to plaintiffs' "need" for the UGDP raw data, or to plaintiffs' position as litigants in the phenformin suspension proceedings. Maj. Op. at 10-11. *See* NLRB v. Sears, Roebuck & Co., 421 U.S. 132, 143 n.10 (1975). My point is simply that, because of the Government's reliance, the UGDP data have been absorbed into the federal decision-making process. This factor, together with the factors previously mentioned—federal funding and federal right of access—satisfies me that the UGDP raw data are agency "records." They should therefore be potentially available for disclosure to *all* members of the public.

[22] Plaintiffs do not challenge the district court's ruling, *see* n.4 *supra*, that the UGDP is not a federal "agency." Pet. Br. at 28 n.7.

could, in limited circumstances, become agency "records." This has been advanced elsewhere as a policy reason for not finding the UGDP data to be agency "records." [23] On closer examination, however, I think even this concern carries little force.

The notion that a chilling effect could result from subjecting the records of federal grantees to disclosure could refer to one of three things. First, it could refer to the possibly inhibiting effect of a visit to the laboratory by a federal official executing a FOIA request. As a basis for restricting FOIA, I find this implausible in the extreme. The inconveniences occasioned by an infrequent FOIA request would be no greater than those currently created by conditions attached to the grant, including the possibility of Government inspection.[24] Yet these burdens appear to have had an imperceptible effect on the enthusiasm for federal research grants.

Secondly, the chilling effect notion could refer to the danger that unscrupulous scientists would use FOIA to appropriate valuable research data for their own credit—or profit. This is a legitimate concern, and if all grantee research records were subject to FOIA it could conceivably deter some scientists from seeking federal grants. But the danger of misappropriation is minimal where, as here, the Government has relied on scientific records in the course of its decisionmaking. Government reliance will likely be limited to cases where the results of the study have been previously published or announced. Thus, whatever weight this concern is entitled to in other contexts, it is of little significance where the element of reliance is present.

[23] Ciba-Geigy Corp. v. Mathews, *supra* n. 3 at 530.

[24] As noted above, HEW grant regulations already give the Government an unlimited right to inspect grantee records. *See* pp. 7-8 *supra*. This right was in fact exercised in this case when the FDA audited the UGDP data.

Finally, federal grant applicants might be inhibited by having methodological or investigatory flaws in their work uncovered through a FOIA request. If *this* is the danger the majority seeks to avoid under the guise of protecting grantee "autonomy," then it is a sad day for both the scientific community and the Freedom of Information Act. The essence of the scientific community, I had thought, is the commitment to the advancement of scientific truth by subjecting findings and conclusions to the "exacting scrutiny of fellow experts." [25] Moreover, where scientific data bear the earmarks of agency "records" subject to FOIA, it would be the height of irony to deny disclosure on the ground that it could expose errors or frauds and thereby discourage those who do the work of the Government. FOIA was enacted in part to end the practice of withholding information "only to cover up embarrassing mistakes or irregularities. . . ." S.REP. No. 813, *supra*, at 3. To restrict the definition of agency "records" to accomplish the same end could only be regarded as a giant leap backwards.

I respectfully dissent.

[25] R. MERTON, THE SOCIOLOGY OF SCIENCE 275 (1973); *see also* B. BARBER, SCIENCE AND THE SOCIAL ORDER 89 (1952).

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 76-1308

PETER H. FORSHAM, et al., APPELLANTS

v.

JOSEPH A. CALIFANO, JR., Secretary of the Department of Health, Education and Welfare, et al.

On Petition for Rehearing

Filed October 17, 1978

Before: BAZELON, LEVENTHAL and MACKINNON, *Circuit Judges*

ORDER

Upon consideration of appellants' petition for rehearing, it is

ORDERED, by the Court, that the aforesaid petition for rehearing is denied.

Per Curiam

Circuit Judge Bazelon voted to grant rehearing for the reasons set forth in the attached statement.

Statement of BAZELON, *Circuit Judge, as to why he voted for rehearing*: In their petition for rehearing, the physicians who requested the UGDP data point out the unusual degree of federal involvement in the initiation and conduct of the UGDP study, which, even under the approach taken by the majority, would bring these data within the scope of "agency records." Specifically, plaintiffs suggest that rather than an independently conceived project by scientists who "developed their own methodology," *see* Maj. op. at 20, the UGDP study was in fact initiated by NIH, which was responsible for developing the research protocol. Petition for Rehearing at 4. Moreover, as a condition of the renewal of the UGDP grant, NIH established a Policy Advisory Board, which, according to plaintiffs, "took initiatives in directing the course of the [UGDP] study," further evidence of government involvement in the on-going UGDP research. *Id.* at 3-4.

The majority opinion notes that "where records are created by a private entity, we believe the applicability of FOIA will turn on whether the government is involved in the core planning or execution of the program." Majority op. at 16. Plaintiffs make a strong case that, from the inception of the study, the government involvement in planning and execution has been pervasive.

Thus, in addition to the reasons set forth in my dissenting opinion, plaintiffs' contentions might well furnish an additional basis for finding these data to be "agency records." Plaintiffs could not previously have known precisely what showing was required under the majority's novel criteria for determining whether the data were agency records.[1] They have now raised a significant

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[1] According to the majority, government involvement in the "core" of a program, see Maj. op. at 16 n.19, 21 is the key to determining whether records created by private individuals or groups are "agency records", which appears to be the first use of that concept in connection with the definition of agency

factual question which, under the majority's approach, warrants a remand to determine the degree of NIH involvement in the initiation and conduct of the UGDP study, rather than an affirmance of the district court, which had focused exclusively on the physical possession and ownership of records.[2]

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records under FOIA. *Cf.* Ciba-Geigy Corp. v. Mathews, 428 F. Supp. 523 (S.D.N.Y. 1977) where the district court, considering another FOIA request for the UGDP data noted that "[t]here is little official authority to aid the Court in discerning whether documents are agency records." *Id.* at 529. It is noteworthy that the principal authority which "lighted" the majority's path was not even a FOIA case, but an action under the Federal Tort Claims Act. See Maj. op. at 12-13, discussing United States v. Orleans, 425 U.S. 807 (1976).

[2] Admittedly, the contentions raised in the petition for rehearing are somewhat conclusory. If, however, the plaintiffs lack factual support sufficient to show government involvement in the core of the program, the district court will then be justified in dismissing the suit.

A far less satisfactory course would be to permit plaintiffs to elaborate their contentions on rehearing in this court. Such supplementation would not consist of adducing evidence, but would more closely resemble a proffer, designed to permit us to assess whether a remand in lieu of affirmance would be any more than a formal gesture. I believe that this approach is inferior to directly remanding this case to the district court because the questions involved are largely factual, and to explore them here may work substantial prejudice to both sides by denying them the opportunity to develop the relevant facts through further investigation, discovery and stipulation in the district court. Only with such a record can a court adequately judge the degree of NIH's involvement in the "core" of the UGDP study. However, I do not believe that we should cut off all avenues for the plaintiffs to show the requisite degree of government involvement in initiating and directing the UGDP study, and therefore I voted for rehearing.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Civil Action No. 76-1308

PETER H. FORSHAM, *et al.*, *Appellants*

v.

JOSEPH A. CALIFANO, JR., *et al.*

APPELLANTS PETITION FOR REHEARING, AND IN THE ALTERNATIVE, SUGGESTION FOR REHEARING IN BANC *

1. (Concise Statement of Issue and Its Importance)

At issue in this case is whether records derived from scientific research planned, financed and controlled by one government agency ad forming the basis for action by another government agency are not "agency records" under the Freedom of Information (FOI) Act, merely because the records are not housed within the physical confines of either agency. The records sought are the product of the University Group Diabetes Program (UGDP) study, a sixteen year study of diabetic patients and the effectiveness and hazards of various forms of treatment of these patients.

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* Also submitted today for the consideration of the Court is Appellants' Motion to Protect Documents. Due to the completion of the UGDP study and the continued serious charges lodged against the coordinating center's handling of the data, there is a danger that the data which is the subject of this action may be destroyed. Such destruction would alienate Appellant's challenge of regulatory action based on the UGDP study data.

Filed today with the Clerk of the Court is a Motion for Expedited Hearing in *Forsham et. al.* v. *Califano* (U.S. Ct. App. D.C. Cir. No. 77-2072). This case involves agency action based on the UGDP study wherein production of the underlying data is a principle issue.

The records, or raw data of the UGDP study are a non-replicable public resource which are of great value to the nation's ten million diabetic patients. Whether this study's published results are truly consistent with the underlying clinical data is a question which has critical ramifications for diabetic patients.

Diabetes Mellitus is a progressive degenerative disease which dictates that treatment for the condition is a continual, daily battle to combat its effects. The UGDP study, through its published reports, would reach into the daily lives of each diabetic patient in the United States and foster a reliance on different modes of treatment. Every one of the presently available treatment modalities comes within the scope of the UGDP study. The results of the study have been and continue to be the subject of Federal regulatory action requiring changes in the diabetic patient's treatment regime.

Leading medical experts dispute the credibility of UGDP published reports. Serious charges of improprieties in the handling of the data continue to be lodged, even by grantee-investigators of the UGDP study itself. The requested public access, whether by confirming the study's results and removing doubts as to its reliability or by altering its conclusions and properly aligning life-saving diabetes therapy, would be of incalculable benefit to present and future victims of the disease.

The Court, in denying public access to the UGDP data, was apparently unaware of the extent to which the UGDP study was the product of government planning and operational control. Facts of the UGDP study relevant to a decision based on the new legal criteria for FOIA production in the Opinion of the Court have not been considered by the Court. Therefore, Appellants direct the Court's attention to the following factors which dictate a reconsideration of the request for public access to the UGDP study data.

2. Appellant-physicians are researchers who have received Federal grants to support their work. This background leads Appellants to appreciate the concern which the Court expressed for the independence and detachment from the government which the private researcher brings to his or her work. The autonomous grantee principle enunciated by the Court is deeply valued by Appellants. However, the UGDP study, as demonstrated below, was not the endeavor of an autonomous grantee.

(a) G. Donald Whedon, then Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), is cited by the Court (Opinion of the Court at p. 5) as describing the normal National Institutes of Health (NIH) grant situation as follows: "Supervision of the grantee's funded activities by this Institute is generally limited to review of periodic reports submitted by the grantee." However, for the UGDP study, NIH instituted a "Policy Advisory Board" as a condition for the renewal of the grant. This policy board was headed by Thomas C. Chalmer, M.D., an employee of NIH who had his offices at NIH and reported to the Director of NIH. With this in-house NIH leadership, the policy board took initiatives in directing the course of the study.

The clear governmental regulatory objective is also evident with the institution of the Policy Advisory Board. The policy board control of the study coincided with FDA application of the study results. The two factors of government control and regulatory use were closely linked in the UGDP study.

(b) Dr. Whedon of NIAMDD also stated "Furthermore, it is *not the normal practice* of NIH or this Institute to require grantees to submit their raw data for review and, in fact, submission of raw data to the Institute is *extremely rare.*" (emphasis supplied) (Opinion of the Court, at p. 5) However, the UGDP study was not a normal NIH grant situation. NIH did require the UGDP co-ordinating center

to cooperate with the Biometric Society, an NIH contractor, to review the study data. The FDA, operating as the agent of NIH sent a team of investigators to the coordinating center to study the warehoused raw data. Defendants in this suit would deny the Plaintiffs access to the data because the data was so conveniently warehoused and located only several miles from NIH and FDA that actual removal of the raw data to government offices was not necessary.

(c) NIH's control over the study included initiation of the plan of research through a two year planning grant. The protocol of the study was the result of an NIH investment. The 12 UGDP university centers were carrying out a government program of research and the UGDP co-ordinating center was administering the study and storing the raw data. The resulting data at the co-ordinating center is not similar to the raw data of an autonomous grantee.

(d) The Opinion of the Court states, "Obviously a government agency cannot circumvent FOIA by transferring physical possession of its records to a warehouse or like bailer." However, just this kind of warehousing is involved with the UGDP co-ordinating center.

The Division of Epidemiology and Biostatistics of the Institute of International Medicine at the University of Maryland, the UGDP co-ordinating center, consisted of sixteen individuals whose primary duties involved co-ordinating federal grant research. The center also co-ordinated the NIH funded "Coronary Drug Project", serving as the data collection point for 53 clinical centers for nine years. The "Coronary Drug Project Aspirin Study" was a similar endeavor in which the Maryland center stored data on 1500 patients in that study. Additionally, the center served the same function as a data repository in the Diabetes Retinopathy Study, which involved 15 clinical centers and approximately 1600 patients. The UGDP study shared with the Diabetes Retinopathy Study its own office facilities that

were rented off campus and housed only these NIH funded activities. No patients were seen at the co-ordinating center.

Administrative storage and warehousing was the raison d'etre for the co-ordinating center.Where, as here, the subject of an NIH grant is to collate and store data for analysis, public access does not violate the legitimate concerns of the grantee and, in fact, serves the purpose of the government funding.

3. For procurement of continued funding in 1975, the UGDP co-ordinating center submitted an Application for Supplemental Grant, in which study "close-out procedures" were outlined. These procedures stated that:

> Once the UGDP investigators have completed their analyses, *the study data should become available for use by any qualified investigator.* In order for data to be available for use outside the UGDP, a group of UGDP investigators should be appointed to assume responsibility for reviewing and approving requests for data and for supervising the preparation and documentation of data tapes, disks, etc. Careful formulation and implementation of such procedures are necessary to assure proper distribution and utilization of study data. (Emphasis supplied)

These statements of the co-ordinating center demonstrate that public access to the raw data was to be a part of the grant plan. Far from eroding the concept of the autonomous grantee, Court ordered access would carry out the principles of scientific accountability which the UGDP itself acknowledged was a condition of the grant.

4. On page 12, the Opinion of the Court states that, "Insofar as it [HEW] is enagaged through FDA, in a regulatory program, it may be subject to requirements of revelation which go beyond the FOIA's rules that govern all agencies. The FDA's regulatory actions are not before us in this FOIA lawsuit. . . ."

Appellants assert that FDA's regulatory actions are before the Court and impact on this FOIA request. The Commissioner of the FDA is a named party to the case and exercised the raw data audit rights of NIH as their agent. The FDA has relied on the study results for regulatory action affecting millions of diabetic patients. Additionally, if the UGDP grant funds had originated from the FDA, rather than its sister agency, NIH, the raw data of the study would be agency records under FDA regulation (21 C.F.R. 20.105(d)). In this case, where HEW through the FDA has applied the results of the study, and possessed the raw data of the study at the co-ordinating center, HEW would deny appellants access to the data because its other arm, NIH, funded the study. This theory would allow the government to limit the rights of the public through changing agency hats to fit the occasion.

It should be noted that the FDA does not shrink from the task of allowing public access to large numbers of documents from a scientific study. The Opinion of the Court therefore erred in placing undue weight on the "awesome implications" of such public access, especially in this case involving a unique set of facts and a 16 year non-replicable study.

5. Cases cited in the Opinion of the Court are not relevant to the facts of this case. *United States* v. *Orleans*, 425 U.S. 807, (1976) dealt with Federal tort liability, not the policy for disclosure of agency records. *NLRB* v. *Sears, Roebuck & Co.* is similarly not applicable here as no request has been made for the creation of agency records by Appellants. Since the requested records in the UGDP study are conveniently stored in a bank vault, copying of the records is a purely ministerial chore, unlike the situation in *NLRB* v. *Sears, Roebuck & Co.*

6. The Concurring Opinion, at page 2, states that no public harm will result from the denial of public access to UGDP data in view of the availability of subpoena au-

thority. However, the shortcomings of this suggested alternative and the further litigation it contemplates reinforces the importance of FOI access in this case. The situation with phenformin is illustrative. On July 25, 1977, the Secretary of Health, Education and Welfare declared phenformin an imminent hazard and summarily banned it from general use without prior hearing or disclosure of any of the raw data on which the order was based. This order was carried throughout the medical and lay press and caused confusion and alarm for thousands of diabetic patients and their physicians. While this order was challenged by appellants and others in concurrent administrative and judicial proceedings, these challenges are still pending at the present time, and no final decisions have been rendered.[1] In short, a full year after nearly all diabetics were required to be removed from phenformin on the basis of the UGDP, no forum—either administrative or judicial—has determined the merits of appellants' challenge to the order and in the context of that challenge, appellants' right to the UGDP raw data. Thus while after-the-fact litigation may theoretically be an alternative way of securing access to the data, it lacks the timeliness and expeditiousness of an FOI request as well as the capacity to prevent needless confusion, alarm and changes in treatment among diabetics and their physicians.

What appellants seek here through FOIA is to determine the validity of the UGDP study *before* further preemptory action is taken by the Government, not to wait for such action to occur and then challenge it after the fact. To require the public to await agency action and then sue the

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[1] The phenformin administrative hearing process (Docket No. 77N-0150) is still ongoing due to the failure of FDA to issue a final ruling. Also pending are Appellants' challenge to the phenformin suspension order, *Forsham et. al.* v. *Califano*, at the District Court for the District of Columbia (No. 77-1478) and, on appeal to the Court of Appeals for the denial by the District Court of preliminary injunctive relief (No. 77-2072).

Government in order to learn of the basis for the Government's action, often taken without benefit of prior hearing, is antithetical to the fundamental principles of FOIA.

Respectfully submitted,

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